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Effects of Physical Activity on Cognition in Persons with Multiple Sclerosis

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Effects of Physical Activity on Cognition in Persons with Multiple Sclerosis

by

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Dedication

I dedicate this to my beloved husband, Philip W. Morrison, and our two daughters, Kelly Anne and Stephanie Lynn, for their love, understanding, and continuous support throughout my educational journey.

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Effects of Physical Activity on Cognition in Persons with Multiple Sclerosis

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Multiple sclerosis (MS), the most common neurological disease among young adults, has an unpredictable course characterized by disparate motor, sensory, and cognitive symptoms. Over half of those with MS experience significant cognitive impairment that adversely impacts role functioning and employment. Since few treatment options exist, research relating physical activity to better cognitive performance in older adults provided support for a comparable linkage between greater physical activity and better cognitive functioning in persons with MS.

The purpose of this study was to determine the feasibility and effects of a physical activity program on measures of clinical cognitive function, perceived cognitive abilities and concerns, and neurocognitive function in everyday life in ambulatory adults with MS experiencing cognitive problems. This quasi-experimental study investigated the effects of a six-month long program of combined aerobic exercise and strength training that met twice weekly for 60-minutes to an attention-control condition of stretching and relaxation that similarly met twice-a-week for 60 minutes for six months. The sample (N=16) of persons with MS consisted of mostly married, White, non-Hispanic females aged 31 to 58 with average disease duration of 11.5$\pm$8.3 years and average EDSS score of 4.5$\pm$1.1.

This dissertation study provided initial evidence of the feasibility of a nurse-led community-based physical activity intervention. While no statistically significant interactions, between or within-group effects were found in this small sample size study, effect sizes were observed that might be used in future studies examining the effect of physical activity on cognitive function in persons with MS.

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Chapter 1: Introduction

Over 400,000 Americans and 2.3 million persons worldwide are diagnosed with multiple sclerosis (MS), the most common neurological disease of adults 20 to 50 years old (NMSS, 2013; MSIF, 2013). This chronic disabling disease of the central nervous system is characterized by cells of the immune system crossing the blood-brain barrier resulting in inflammation and scaring of the myelin sheath, axonal loss, and gray matter atrophy (Trapp et al., 1998). MS has an unpredictable course with disparate motor, sensory, and cognitive symptoms unique to each individual with the disease. Over time, MS leads to limitations in physical and cognitive functioning and varying levels of disability in the majority of individuals.

Significant cognitive impairment is experienced by 43% to 70% of individuals diagnosed with MS (Langdon, 2011). Cognitive impairment in MS varies considerably among individuals and may present in the early stages of the disease; yet is not associated with disease duration and is reported as being more severe in progressive forms of MS (Beatty, Goodkin, Hertsgaard, & Monson, 1990; Chiaravalloti & DeLuca, 2008; Lynch, Parmenter, & Denney, 2005). Impairments in cognition commonly result in deficits of everyday life functions such as driving, managing complex medication regimes, and handling household responsibilities (Schultheis, Garay, & DeLuca, 2001; Kalmar, Gaudino, Moore, Halper, & DeLuca, 2008). While these day-to-day activities are critical to maintaining independence, arguably the most devastating consequence of cognitive impairment in MS is unemployment (Rao, Leo, Bernardin, & Unverzagt, 1991).

Cognitive impairment in MS is regularly under diagnosed and poorly managed leaving patients with few therapeutic options (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008). Research investigating pharmacologic therapies for cognitive impairment in MS has been disappointing (Krupp et al., 2011) and there are no approved medical therapies to treat cognitive symptoms in MS at this time. While disease-modifying treatments for MS have demonstrated efficacy among several medical outcomes (e.g. annualized relapse rate, MRI progression), scant evidence exists to support any positive effects among cognitive outcomes (Amato et al., 2013; Benedict & Zivadinov, 2011). Cognitive rehabilitation research has been mixed (O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008), with computer-assisted cognitive rehabilitation programs showing promise (Mattioli, Stampatori, Zanotti, Parrinello, & Capra, 2010; Shatil, Metzer, Horvitz, & Miller, 2010; Stuifbergen et al., 2012). Recent research building on the science relating physical activity to better cognitive performance in healthy and cognitively impaired older adults supports a relationship between greater physical activity and better cognitive functioning in persons with MS (Heyn, Abreu, & Ottenbacher, 2004; Kramer, Erickson, & Colcombe, 2006; Motl, Gappmaier, Nelson, & Benedict, 2011). This preliminary data suggests the intriguing possibility that improving physical activity in persons with MS, traditionally promoted for its impact on mobility and physical symptoms, might also have important impact on improving cognitive functioning (Motl, Sandroff, & Benedict, 2011).

PURPOSE

The purpose of this study was to determine the feasibility and effects of a physical activity program on measures of clinical cognitive function and neurocognitive function in everyday life in ambulatory persons with MS experiencing cognitive problems. The study builds on existing research suggesting that increases in physical activity may have positive effects on disease activity, functional status, mental and physical health (Stuifbergen, Becker, Blozis, Timmerman, & Kullberg, 2003; Motl, Gappmaier, et al., 2011). The study compared the effects of the Physically Active Lifestyle in MS (PALMS) intervention [a 6-month program of supervised strength and aerobic training two times a week for 60 minutes conducted in supervised small groups (4-5 persons) plus direction to be physically active at home for 30 minutes daily, 3+ days per week] to an attention-control group. The attention-control group program involved twice weekly 60-minute sessions of group relaxation and stretching classes lead by a trained facilitator for 6-months. The specific aims of this exploratory study are to:

Aim #1. Determine the feasibility of delivering a small group moderate-intensity exercise program for persons with MS over a 6-month time period.

Aim #2. Explore the effects of the Physically Active Lifestyle in MS (PALMS) intervention on the primary outcomes of clinical cognitive function (battery of neuropsychological tests), self-reported cognitive abilities and concerns, and neurocognitive function in everyday life (revised Everyday Problems Test, EPT-R) and the secondary outcomes of exercise self-efficacy, physical activity, depressive symptoms, and fatigue.

BACKGROUND AND SIGNIFICANCE

Persons with multiple sclerosis (MS) affected by cognitive impairment experience significant reductions in productivity and participation in family and society defined roles (e.g., breadwinner, caregiver). Cognitive impairment in persons with MS is common and debilitating, yet a void of treatment options exists for those who are affected. Persons with cognitive impairments in MS commonly experience deficits in processing speed, visual learning and memory; deficiencies in attention, information processing efficiency, executive functioning (processing, planning, inhibition, prioritizing), and long-term memory are also reported (Chiaravalloti & DeLuca, 2008). Cognitive impairment in MS has been linked to dysfunction in daily activities, increased demands for assistive care, and loss of independence (Kalmar et al., 2008). Research investigating interventions to improve cognitive function in persons with MS is expanding but there are currently no evidence-based or federally approved protocols to manage the devastating cognitive symptoms associated with MS (Amato, Zipoli, & Portaccio, 2006; O'Brien et al., 2008).

Based on research findings in the field of gerontology, increased physical activity has potential in managing and/or minimizing cognitive impairment in persons with MS (Motl, Sandroff, et al., 2011). Physical activity has been positively related with improved cognition in aging adults, persons with schizophrenia and stroke (Colcombe & Kramer, 2003; Kluding, Tseng, & Billinger, 2011; Knöchel et al., 2012). In addition, a review of the literature on exercise and brain health suggested that physical activity may promote brain health through changes in neuroreactive proteins, immune factors, and stress hormones, which reduce long-term disability through neuroprotection, neuroplasticity,

and neuroregeneration (White & Castellano, 2008a, 2008b). Therefore, physical activity is an attractive modifiable behavioral correlate for improving cognitive functioning in persons with MS.

Research has shown that persons with MS are significantly less physically active than non-diseased populations (Motl, McAuley, & Snook, 2005). Until recently, physical activity was believed to increase MS progression and patients were instructed to rest (Döring, Pfueller, Paul, & Dörr, 2012; Vollmer et al., 2012). A cyclic pattern of increased inactivity, depression, and fatigue resulted in further deconditioning and disablement (MacAllister & Krupp, 2005). This presumed association between physical activity and increased fatigue, depression and MS exacerbation has not been supported by the literature (Pilutti, Platta, Motl, & Latimer-Cheung, 2014; Rietberg, van Wegen, Uitdehaag, & Kwakkel, 2011; Tallner et al., 2012). In fact, a substantial body of research exists supporting the positive effects physical activity has on persons with MS including improvements in mood, muscle function, and mobility (Rietberg et al., 2011; White & Dressendorfer, 2004). However, current research lacks high quality randomized controlled trials on the effects of physical activity on cognition in this same population.

CONCEPTUAL FRAMEWORK

This study and the PALMS intervention it tested are based on Alfred Bandura's self-efficacy theory (1997) and social cognitive theory (1986). Social cognitive theory proposes that learning occurs within a social framework and that dynamic reciprocal relationships exist between personal factors, environmental events and behavior. The influence of any factor in the model on the others is situational: personal factors

(cognitions, beliefs and affect) impact behavior and the environment; behavior affects personal factors and environment; and environmental events influence behavior, thoughts, beliefs and affect in unceasing reciprocal fashion. Humans learn from and adapt to their environment. Social cognitive theory conceptualizes behavior adaptation and modification as a learning process. "Behavior can be changed though new learning experiences, guidance in the adjustment of perceptions, and support for the development of capacities" (Glanz, Rimer, & Viswanath, 2008, p. 176).

Social cognitive theory is based on the concept of human agency, the uniquely human capacity to exercise influence over one's behavior through acts intended to produce desired effects. Human agency and the inherent freedom to make behavior choices operate within a diverse social milieu grounded in social systems, norms and rules. In addition to human agency, social cognitive theory is grounded on the distinctly human capacities to cogitate and communicate symbolically, use forethought to imagine and contemplate future scenarios, learn vicariously by observing others (models), self-regulate their behavior, and self-reflect on thoughts and beliefs. These capabilities coalesce to shape an individual's judgment of their personal capability to successfully enact specific behaviors - self-efficacy.

Bandura (2004) proposes that self-efficacy judgments function jointly with outcome expectations, goals, and sociostructural factors (perceived barriers and facilitators) in regulating human behavior. Self-efficacy has been cited as the most significant predictor of human behavior (McAuley & Elavsky, 2008; Pender, Murdaugh, & Parsons, 2011). Self-efficacy is not a static phenomenon that one has or does not have;

even possessing the skills necessary for a particular behavior does not ensure sufficient confidence to initiate behavior (Bandura, 1997). “Perceived self-efficacy is not a measure of the skills one has but a belief about what one can do under different sets of conditions with whatever skills one possesses” (Bandura, 1997, p. 37). Greater self-efficacy empowers individuals to initiate more challenging behaviors, expend greater effort and persevere despite aversive conditions (Bandura, 1997). Low self-efficacy undermines effort, lessens judgment of capability, and weakens persistence even thwarting attempts of new behavior.

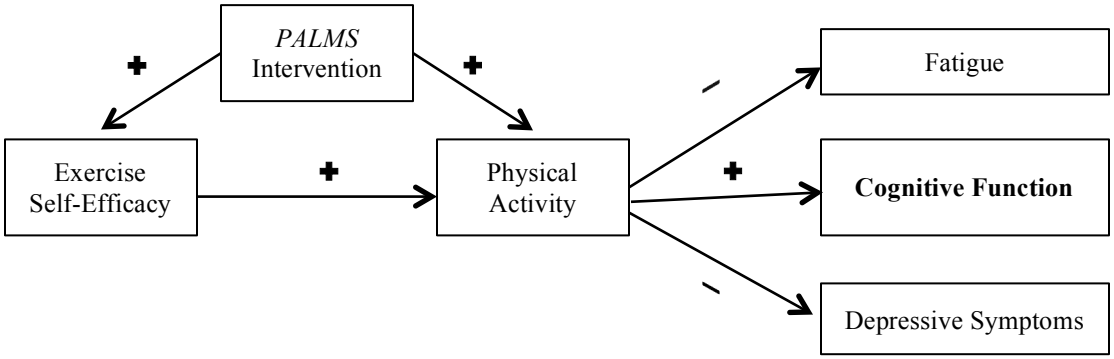
Social cognitive theory identifies four distinct sources of information to develop and foster self-efficacy skills: enactive mastery experiences, vicarious experiences, verbal persuasion and emotional/physiological states (Bandura, 1986). Mastery experiences and prior history of successful behavior are the most potent of the four sources (McAuley & Elavsky, 2008). Mastery experiences that promote self-efficacy strength and generalizability are nuanced. If successes were too easily gained, small failures may undermine existing self-efficacy beliefs. Development of greater self-efficacy is built upon small incremental successes. Mastering these behaviors fosters persistence in the face of difficulty and perseverance to overcome barriers. Vicarious experiences offer learning opportunities from observing others model behavior. Greater similarity between the personal characteristics of the model and the observer inspires greater confidence (McAuley & Elavsky, 2008). Thus, a model with MS-related fatigue who is able to overcome challenging barriers (e.g., fatigue, heat, self-doubt) to walk for 15 minutes a day instills greater efficacy beliefs in an observer with MS than would a healthy young

fitness trainer modeling the exact same behavior. Verbal persuasions from credible and well-informed sources (e.g., personal trainer, coach) can engender greater effort and perseverance (Bandura, 1997). Persuasion must be genuine and emanate from trustworthy sources to increase self-efficacy. Physical and emotional state can affect self-efficacy positively or negatively. Depression, anxiety, lack of rest, and hunger can be deleterious to self-efficacy beliefs. Persons with MS may have difficulty discriminating between fatigue related to physically activity and fatigue related to their MS. Somatic symptoms such as sweating and breathing heavily, indicators of exercise intensity, may be interpreted negatively as harbingers of "overdoing it" (McAuley & Elavsky, 2008).

The focus of the present study, physical activity, is a specific type of health promoting behavior. Physical activity behaviors are influenced by the individual's capability to learn and perform the new behavior, modeling of behavior (especially by like individuals), positive and negative reinforcement, outcome expectations, and self-efficacy. Physical activity behavior is strongly influenced by self-efficacy – the belief in one's ability to successfully engage in the target behavior. Self-efficacy has been described as a pivotal factor in facilitating physical activity behavior in persons with MS (McAuley et al., 2007; Motl, McAuley, Doerksen, Hu, & Morris, 2009). The *PALMS* intervention, using social cognitive theory determinants and structural pathways, proposes to foster exercise self-efficacy and boost physical activity behavior through modeling of appropriate exercise behavior, increased social support, positive verbal persuasion (coaching) and management of emotional and physiological state. It is then hypothesized that increased physical activity behavior will positively affect cognitive

function, and reduce depressive symptoms and fatigue. The conceptual model used for the current study is illustrated in Figure 1.

Figure 1. PALMS Theoretical Model



SUMMARY

Research guided by social cognitive theory and its determinants provided a comprehensive and well-supported conceptual framework for exploring the effects of physical activity on cognitive function in persons with MS. Social cognitive theory has been broadly applied in empirical studies of health-promotion and physical activity behavior among diverse populations including: physical activity and function in older adults (McAuley et al., 2012), physical activity in middle and older adults (White, Wójcicki, & McAuley, 2012) exercise in older women (Conn, Burks, Pomeroy, Ulbrich, & Cochran, 2003), and physical activity in older adults at risk for Alzheimer disease (Lautenschleger et al., 2008). A recently published review stated, "the most widely used

theory for physical activity and MS is social cognitive theory and its constructs" (Dixon-Ibarra, Vanderbom, Dugala, & Driver, 2014, p. 153). Intervention studies aimed at improving cognitive function in persons with MS by increasing physical activity behavior are rare. Social cognitive theory was selected as the theoretical framework for the current study based upon its application to the design of intervention studies exploring health promotion and physical activity in persons with MS (Stuifbergen et al., 2003; Dlugonski, Motl, & McAuley, 2011). In this intervention study, determinants derived from social cognitive theory were used to explore the feasibility and to determine the effects of the PALMS intervention on cognitive function outcomes, depressive symptoms, and fatigue.

RESEARCH QUESTIONS AND HYPOTHESES

The specific research questions addressed in this non-randomized controlled trial were:

RQ 1.

What is the feasibility of delivering a small group moderate-intensity exercise program for persons with MS over a 6-month time period?

RQ 1.1.

What is the pattern of response to and enrollment in the study?

RQ 1.2.

What is the attendance pattern across the 6-months for the intervention and attention-control groups?

RQ 1.3.

What is the frequency, duration, and mode of physical activity documented in the PALMS physical activity log?

RQ 1.4.

How do the participants respond to the PALMS intervention (heart rate, ratings of perceived exertion, physical and mental fatigue, general wellbeing, and enjoyment)?

RQ 2.

What are the effects of the Physically Active Lifestyle in MS (PALMS) intervention?

RQ 2.1.

What are the within-group, between-groups, and group-by-time interaction effects on the primary outcomes of clinical cognitive function (California Verbal Learning Test [CVLT], Brief Visuospatial Memory Test [BVMT], Controlled Oral Word Association Test [COWAT], NIH Toolbox Flanker Inhibitory Control and Attention Test [Flanker], NIH Toolbox Oral Symbol Digit Test [OSD]), self-reported cognitive abilities and concerns (Patient-Reported Outcomes Measurement Information System [PROMIS] v1.0 Cognitive Abilities and Cognitive Concerns Scales), and neurocognitive function in everyday life (revised Everyday Problems Test [EPT-R]) (Benedict, 1997; Benton, Sivan, Hamsher, Varney, & Spreen, 1994; Cella et al., 2007; Delis, Kaplan, & Kramer, 2000; Weintraub et al., 2013; Willis, Jay, Diehl, & Marsiske, 1992)?

RQ 2.2.

What are the within-group, between-groups, and group-by-time interaction effects on the secondary outcomes of exercise self-efficacy [ExSE], physical activity [GLTEQ and accelerometer counts: sedentary, light, moderate-to-vigorous physical activity, and

steps], depressive symptoms [CES-D], and fatigue [MFIS] (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Godin & Shepard, 1985; McAuley, 1993; Pearson, Busse, van Deursen, & Wiles 2004; Radloff, 1977)?

Hypothesis 2.1.

Primary outcome measures (clinical cognitive function, self-reported cognitive abilities and concerns, and neurocognitive function in everyday life) will be significantly improved at 3 and 6-months over baseline in the intervention group compared to the attention-control group.

Hypothesis 2.2.

Secondary outcome measures (exercise self-efficacy, physical activity, depressive symptoms, and fatigue) will be significantly improved at 3 and 6-months over baseline in the intervention group compared to the attention-control group.

DEFINITION OF TERMS

The following definitions were used for this study.

1. Cognitive Function

Conceptual definition. Cognitive functions encompass the human mental activities of thinking, learning, and memory (Pugh et al., 2006). Domains of cognition commonly affected in persons with MS include: sustained and complex attention, concentration, working and secondary memory, information processing speed, visiospatial skills, verbal fluency, and executive function – planning, organization, judgment, reasoning, problem solving (Amato et al., 2013; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; LaRocca, 2000).

Operational definition. Scores on tests of clinical cognitive function - California Verbal Learning Test [CVLT], Brief Visuospatial Memory Test [BVMT], Controlled Oral Word Association Test [COWAT], Flanker Inhibitory Control and Attention Test [Flanker], Oral Symbol Digit Test [OSD], self-reported cognitive abilities and concerns [PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales], and neurocognitive function in everyday life - revised Everyday Problems Test [EPT-R] (Benedict, 1997; Benton et al., 1994; Cella et al., 2007; Delis et al., 2000; Weintraub et al., 2013; Willis et al., 1992).

2. Depressive Symptoms

Conceptual definition. Depressive symptoms are the major indicators commonly associated with the mental health disorder depression, which include unhappy feelings and/or perceptions, changes in sleeping behavior and somatic complaints (Kroenke, 2003; Radloff, 1977).

Operational definition. Self-report scores on the 20-item Center for Epidemiologic Studies Depression Scale-Revised (CES-D) (Radloff, 1977).

3. Exercise

Conceptual definition. Exercise is a subcategory of physical activity that is planned, repetitive, structured, and goal oriented (Caspersen, Powell, & Christenson, 1985).

Operational definition. PALMS intervention dose - measured by the number of sessions attended, rating of perceived exertion and heart rate recorded via chest-strap at ten-minute intervals throughout the 60-minute session.

4. Exercise Self-Efficacy

Conceptual definition. Exercise Self-Efficacy is a person's perceived capability to successfully engage in moderate intensity exercise behavior for 20 minutes or more three times a week for the subsequent one to six months (McAuley, 1993).

Operational definition. Self-report scores on the six-item Exercise Self-Efficacy scale (McAuley, 1993).

5. Fatigue

Conceptual definition. Fatigue is the subjective, multidimensional perception of the absence of physical, cognitive and/or psychosocial energy (MS Council for Clinical Practice, 1998; Rietberg, van Wegen, & Kwakkel, 2010).

Operational definition.

Self-reported scores on the 21-item Modified Fatigue Impact Scale (MFIS) that reports summated total score, as well as physical, cognitive and psychosocial subscale scores (Fisk, Pontefract, et al., 1994).

6. Physical Activity

Conceptual definition. Physical activity is the voluntary movement of skeletal muscles, which results in energy expenditure (Caspersen et al., 1985).

Operational definition. Physical activity will be estimated using two measures: 1) self-report scores on the two-item Godin Leisure Time Questionnaire (GLTQ) and 2) mean daily activity counts (sedentary, light, moderate-to vigorous) and step counts downloaded from waist-worn accelerometers (ActiGraph™, 2016; Godin & Shepard, 1985).

ASSUMPTIONS

Assumptions of the present study include:

1. Participants have an accurate diagnosis of MS.

2. Persons with MS want to increase their physical activity level.

3. Improvements in or maintenance of cognitive function (neuroplasticity) is feasible in persons with MS.

4. Social cognitive determinants (self-efficacy, outcome expectancy, perceived barriers and facilitators) influence engagement in physical activity behavior.

5. Increased physical activity has the potential to affect cognitive function either directly or indirectly through reduced depressive symptoms and/or fatigue.

6. Participants truthfully and accurately respond to the self-report measures.

7. Physical activity can be validly and reliably documented in ambulatory persons with MS by wearing an accelerometer on the waist.

LIMITATIONS

Possible limitations of the current study include:

1. Results of the study may not be generalized to other persons diagnosed with MS, especially for those requiring the use of an assistive device (e.g., walker, scooter, wheelchair).

2. Participants of this study may not accurately reflect other people with MS who may not be willing or able to participate in research studies involving a six-month physical activity program.

3. The sample size may not be large enough to detect a statistically significant within-group or between-groups difference, or a group-by-time interaction effect.

4. Group assignment in a small sample may not be able to counteract the effect of other variables on the outcomes such as differences among participants in baseline cognition, physical function, or physical fitness.

5. Self-report measures are susceptible to response bias.

6. Measures of clinical cognitive function (designed as diagnostic tools) may not capture or accurately measure change over time.

7. Accelerometers worn for seven days at baseline, 3-months and 6-months may not capture or reflect change in participants' level of physical activity.

SUMMARY

This chapter discussed the background and significance of cognitive impairment in persons diagnosed with MS. The primary purpose of this study was to determine the feasibility and effects of a physical activity program on: 1) primary outcome measures of clinical cognitive function, self-reported cognitive abilities and concerns, and neurocognitive function in everyday life and: 2) secondary outcome measures of exercise self-efficacy, physical activity, depressive symptoms and fatigue in ambulatory persons with MS experiencing cognitive problems. Alfred Bandura's self-efficacy theory (1997) and social cognitive theory (1986) were used as the theoretical framework for this quasi-experimental study. Conceptual and operational definitions of the concepts integral to this study were delineated. Findings from this study may provide critical information on the feasibility of the PALMS intervention (a 6-month long program of supervised, small group strength and aerobic exercise meeting two times a week for 60-minutes) and any effects the intervention had on cognitive function, exercise self-efficacy, physical activity, depressive symptoms, and fatigue in persons with MS experiencing cognitive problems compared to an attention-control condition.

Chapter 2: Review of the Literature[1]

This chapter presents a review of the literature relevant to physical activity and cognition in persons with MS. The review commences with an overview of multiple sclerosis focusing on three significant sequelae of the disease: cognitive impairment, depression, and fatigue. The critical appraisal of these MS-related symptoms includes the number of individuals affected, impact on health, management strategies as well as the interrelationships between the symptoms. The chapter continues with a review of physical activity as a self-management approach to symptom management in persons with MS. The final section of this chapter reviews the effects of physical activity on cognition in older adults as the logical basis for conducting similar studies in person with MS. While experimental studies investigating the effect of physical activity on cognition in persons with MS are few, there is considerable evidence supporting the positive effects of physical activity on cognitive function and brain physiology in healthy as well as cognitively impaired older adults.

MULTIPLE SCLEROSIS

MS is characterized by sporadic bouts of disparate neurologic symptoms disseminated over time and space (McDonald et al., 2001). Symptoms are related to an autoimmune inflammatory process occurring within the central nervous system, resulting in discrete areas of demyelination and destruction of axons in the brain parenchyma

[1] Morrison, J.D., & Mayer, L. (*2016*). Physical activity and cognitive function in persons with multiple sclerosis: an integrative review. *Disability and Rehabilitation*. Advance online publication. doi:10.1080/09638288.2016.1213900. First author conceptualized and designed the paper, gathered and interpreted the data, drafted the manuscript and gave final approval of the submitted version.

and/or spinal cord (O'Conner, 2002). Transmission of neural signals is disrupted in the areas affected resulting in the great variability of symptoms expressed (O'Conner, 2002). The onset of MS symptom expression commonly occurs in young adults between the ages of 20 and 40 (Wallin, Page, & Kurtzke, 2000). Women outnumber men with MS approximately 2.5:1 (Wallin et al., 2000; McDonald et al., 2001). The specific cause of MS has yet to be determined but both environmental and genetic factors are thought to be involved (Wallin et al., 2000). Life expectancy is shortened by approximately 5% in persons with MS with the progressive accrual of disability resulting in great human and economic cost for those affected (Greer & McCombe, 2011; Rao, Leo, Bernardin, & Unverzagt, 1991).

Due to the heterogeneous nature of MS, a standardized classification system was developed to facilitate communication of patients' functional status among clinicians and researchers (Lublin & Reingold, 1996). In this system, MS is categorized into four different forms based on the course of the disease, symptoms expressed, residual functional impairment, and progression of neurological impairment over time (Lublin & Reingold, 1996; NMSS, 2014b; Scalfari, Neuhaus, Daumer, Muraro, & Ebers, 2014). Relapsing-remitting MS, the initial course in 85% of cases, is characterized by discrete episodes of worsening neurologic symptoms followed by a variable return of function and periods of stability between exacerbations (Fox & Cohen, 2001). Secondary-progressive MS follows the relapsing-remitting course when progressive worsening of baseline neurologic symptoms occurs with or without further exacerbations – typically 10 to 15 years after initial MS diagnosis if not treated with disease modifying drugs

(Weinshenker et al., 1989). The conversion rate from relapsing-remitting to secondary-progressive MS of those treated with disease modifying drugs is unclear (Chelune, Stott, and Pinkston, 2008). Primary-progressive MS is distinguished by steadily worsening neurologic symptoms from the onset and nearly continuous gradual functional impairment. Progressive-relapsing MS, the least common form, is characterized by progressive neurologic impairment and deterioration from the start with sporadic exacerbations and variable recovery of function between acute relapses (Lublin & Reingold, 1996; NMSS, 2014b; Scalfari et al., 2014)

MS-Related Symptoms

MS symptoms, manifestations of neurologic pathology, are widely diverse and follow an unpredictable fluctuating course. While motor symptoms such as spasticity and foot drop are readily apparent, many symptoms of MS are not visible to others (e.g., weakness, dizziness, cognitive and emotional changes) but are instrumental to functional status and disability. To systematically evaluate functional status and disability in persons with MS, Kurtzke (1983) developed the Expanded Disability Status Scale (EDSS) using a framework of eight functional groups: visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral, and ambulation. A criticism of the widely used EDSS is that the total score is heavily weighted on ambulatory status and fails to reliably capture the effect of MS on cognitive and sensory functions (Cohen, Kessler, & Fischer, 1993).

The cerebral function group consists of depression, decrease in mentation, and fatigue. This group of neurologic functions is singled out for their pervasiveness and profound influence on functional status, disability and quality of life in persons with MS.

COGNITIVE IMPAIRMENT IN PERSONS WITH MS

Charcot documented distinctive cognitive deficits in persons with MS as long ago as 1877, yet research investigating this phenomenon was scarce until the early 1990's and the work of Stephen Rao (Charcot, 1877; Chelune et al., 2008; Messinis, Kosmidis, Lyros & Papathanasopoulos, 2010). Rao reported that significant cognitive impairment was experienced by over half of those diagnosed with MS (Rao, Leo, Bernardin, & Unverzagt, 1991). The scarcity of literature exploring cognitive impairment in persons with MS prior to the early 1990s has been attributed to the subtle onset and slow progression of MS-related cognitive impairment, especially when compared to dementia, as well as the focus of clinicians and patients being drawn to the more conspicuous physical impairments of MS (Chelune et al., 2008; Messinis et al., 2010). Research exploring cognitive function in persons with MS was propelled forward by the development of specific guidelines in 2001 that included magnetic resonance imaging in the diagnostic criteria for MS and approval by the U.S. Food and Drug Administration of the first disease modifying drug (interferon beta-1b) in 1993 (McDonald et al., 2001; NMSS, 2014a). Together, these advances allowed clinicians a long awaited therapeutic option to slow down the frequency of exacerbations, progression of pathology and accumulation of disability as well as a powerful non-invasive method to visualize the extent and pattern of MS pathology in vivo.

Cognitive impairment in MS differs substantially from person to person and may present at any stage of the disease - even at the onset (Amato et al., 2006; Beatty et al., 1990). While cognitive impairment is rarely a presenting symptom of MS, it may be

present early in the disease when physical function is minimally affected (Chelune et al., 2008; Haase, Tinnefeld, Lienemann, Ganz, & Faustmann, 2003; Olivares et al., 2005; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). While Benedict and Bobholtz (2007) report that MS-related dementia is rare (perhaps less than 25% of those diagnosed), Westervelt (2015) describes a dearth of literature on MS-related dementia, which may be due to due to lack of clarity about the meaning of the term "dementia" in this population. The impact of impaired cognition function negatively affects the person with MS, their family and caregivers alike; commonly straining everyday household responsibilities, work status, and social functioning (Schultheis et al., 2001; Kalmar et al., 2008). Individuals with moderate to severe cognitive impairment may experience substantial difficulty with activities of daily living and require assistance with personal care (Benedict et al., 2005; Rao, Leo, Ellington, et al., 1991). Perhaps the most detrimental of all of the consequences of MS-related cognitive impairment is the loss of employment and the harsh economic impact it has on the individual and their family (Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008).

MS NEUROANATOMY AND PATHOLOGY

The neuroanatomical changes related to MS pathology and the mechanisms underlying cognitive impairment have not yet been fully explained but considerable knowledge has been garnered from advances in imagining technology and techniques (Guimarães & Sá, 2012). While MS has traditionally been considered a white matter disease, gray matter changes have become the focus of research using new quantitative imaging techniques such as magnetization transfer imaging, diffusion tensor imaging, and

proton magnetic resonance spectroscopy (Messina & Patti, 2014). White matter in the brain consists of collections (tracts) of myelin-encased axons, the long cylindrical output processes of nerve cells that travel between and within the brain's hemispheres transferring nerve impulses between neurons and connecting cortical and subcortical gray matter (Chelune et al., 2008). Gray matter consists of the neuron's cell body and short receiving extensions (dendrites) located in the cerebral cortex (surface) and in deep subcortical structures such as the thalamus, hypothalamus, and hippocampus (Chelune et al., 2008).

MS-related cognitive impairment has been associated with white matter lesion burden (Chiaravalloti & DeLucca, 2008; Rovaris, Comi, & Filippi, 2006). Stronger relationships have been reported between tests of neurocognitive function and different measures of brain volume in persons with MS: whole brain, deep gray matter (thalamus), cerebral cortex, and corpus callosum (Amato et al., 2004; Benedict, Bruce, et al., 2006; Houtchens et al., 2007; Rao et al., 1989; Simon et al., 1999). The hippocampus, a deep gray matter structure, has been the target of study in persons with MS due to its involvement with memory function (Prakash, Patterson, Janssen, Abduljalil, & Boster, 2011). In two cross-sectional studies, third ventricular volume was shown to be a consistent predictor of neuropsychological function in MS (Benedict, Weinstock-Guttman, et al., 2004; Benedict, Bruce, et al., 2006).

MS NEUROIMAGING

Traditional magnetic resonance imaging (MRI) using T2-weighted and Gadolinium enhanced T1-weighted images are used in the diagnostic process, measures

of brain volume (atrophy) and lesion burden (Rovaris et al, 2006). Newer MRI techniques allow researchers to investigate normal appearing white matter using fractional anisotropy (FA), a diffusion tensor imaging parameter that reflects fiber integrity and alignment (Filippi et al., 2010, Guimarães & Sá, 2012). Studies have correlated tract damage, decreased FA in the corpus callosum, with impaired attention, speed of information processing, and working memory in persons with MS (Dineen et al., 2009, Roosendaal et al., 2009). Proton magnetic resonance spectroscopy allows in vivo assessment of key biochemical data from a specific location called a voxel (Kurth & Bigler, 2008). Increased choline peaks mark high cell membrane turnover suggestive of cell death or rapid cell division and N-acetylaspartate (NAA) levels are associated with neuronal and axonal viability (Filippi et al., 2010). Two studies have associated NAA with measures of attention and memory in persons with MS (Gadea et al., 2004; Staffen et al., 2005).

MS-RELATED NEUROCOGNITIVE RISK FACTORS

Several factors have been associated with higher risk of developing cognitive impairment in MS including advancing age, male gender, disability status, below average intelligence and low educational attainment (Benedict & Zivadinov, 2011; Haase et al., 2003; Messinis et al., 2010). Cognitive impairment has been associated with disability status, low level of education, and disease duration among men but not women in a study of 563 patients with MS (Savettieri et al., 2004). Sartori and Edan (2006) reported that among 40 patients with MS, age (greater than 40) and low education level (less than 11 years) were associated with cognitive deficits. Men tend to have earlier onset and a more

aggressive course of MS than women and be particularly vulnerable to cognitive impairment (Beatty & Aupperle, 2002; Chelune et al., 2008; Greer & McCombe, 2011).

Cognitive impairment has also been related to disease course such that secondary-progressive MS is consistently associated with greater risk than the relapsing-remitting or primary-progressive MS courses (Amato et al., 2006; Chiaravalloti & DeLuca, 2008; Lynch et al., 2005). Perhaps surprisingly, studies do not support more than weak associations between MS-related cognitive impairment measured with neuropsychological tests and perceived fatigue, length of diagnosis, or depression (Arnett, Barwick, & Beeney, 2008; Benedict & Zivadinov, 2011; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). Benedict & Zivadinov (2011) attribute these paradoxical relationships to the considerable heterogeneity found in MS-related cognitive impairment.

NEUROCOGNITIVE DOMAINS AFFECTED IN MS

Domains of cognition often impaired in persons with MS include: attention, short and long-term memory, information processing speed, visiospatial skills, and executive function – planning, organization, judgment, reasoning, problem solving (Amato et al., 2013; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008). Of these, visual learning, memory, and processing speed are the most frequently affected cognitive domains in persons with MS (Chiaravalloti & DeLuca, 2008). One recent study suggests that not only is impaired processing speed the most common cognitive deficit among persons with MS, it is often the first deficit to present clinically (Van Schependom et al., 2014). Intelligence is reported to remain relatively unimpaired in those with MS but verbal

intelligence measured with the Wechsler Adult Intelligence Scale-Revised was significantly lower ($p < .001$) in a sample of persons with MS than normal controls (Rao, Leo, Bernardin, & Unverzagt, 1991).

MS NEUROCOGNITIVE ASSESSMENT

Cognitive impairment in MS is regularly under diagnosed and poorly managed leaving patients with few therapeutic options (Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008). Routine evaluation of cognitive function is advocated to detect deficits early on, monitor disease progression and provide documentation for work disability but substantial barriers (e.g. cost, time and expertise needed) impede early and routine assessment of cognitive function in persons with MS (Amato et al., 2013; Benedict & Zivadinov, 2011; Messinis et al., 2010). Regrettably, once cognitive function is impaired in persons with MS, improvement has been difficult to achieve despite therapeutic intervention (Amato et al., 2006). While the patient's perception of cognitive deficits is integral to clinical assessment, self-report measures of cognitive impairment are apt to overstate cognitive impairment in those who are depressed and may go unnoticed in those with significant cognitive impairment (Kinsinger, Lattie, & Mohr, 2010). Self-reports of cognitive difficulty strongly relate to depressive symptoms ($r = 0.61$) when compared to caregiver-reports ($r = 0.37$) (Benedict, Cox, et al., 2004). Additionally, fatigue confounds perceptions of cognitive impairment in patients with MS; greater fatigue has been linked with self-reported cognitive deficits yet there is little association between fatigue and neuropsychological measures of cognitive impairment (Kinsinger et al., 2010).

Two psychometrically sound neurocognitive batteries are widely used by highly trained neuropsychologists to assess cognitive function in MS– the Brief Repeatable Battery of Neuropsychological tests (BRBN) and the Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002; Rao et al., 1990). While the two batteries are quite similar and have considerable test overlap, there are also differences. The BRBN is older and has been more widely used while the newer MACFIMS assesses additional cognitive domains and has alternative forms for three of the seven tests (Guimarães & Sá, 2012; Strober et al., 2009). The BRBN consists of five neurocognitive tests assessing auditory processing speed, working memory, visual processing speed, auditory and spatial episodic memory, and expressive language (Benedict & Zivadinov, 2011). The seven test MACFIMS assesses spatial processing and executive function in addition to the domains included in the BRBN (Benedict et al., 2002). Unfortunately, these batteries were not developed to monitor change in cognitive function over time or to define change in everyday cognitive function that is crucial to patients, clinicians and researchers alike (Becker, Stuifbergen, & Morrison, 2012).

More recently, a consensus committee comprised of neurologists and neuropsychologists with expertise in MS has recommended a three-test cognitive monitoring tool - the Brief International Assessment of Cognition for MS [BICAMS] (Langdon et al., 2012). The objective of the panel was to recommend a psychometrically sound test battery that 1) could be administered by any healthcare professional without specific assessment training, 2) be completed in approximately 15 minutes, 3) doesn't require special equipment, and 4) encompassed the cognitive domains of "information

processing speed, verbal memory and visual memory…as these three domains would capture a reasonable proportion of significant cognitive impairment in large clinical settings" (Langdon et al., 2012, p. 893). Tests assessing executive function were not included in the battery as the committee considered these types of test "too long and too challenging to administer in the target context" (Langdon et al., 2012, p. 893). The three tests of the BICAMS are: the Symbol Digit Modalities Test [SDMT] (Smith, 1982), the California Verbal Learning Test-II [CVLT-II] (Delis et al., 2000), and The Brief Visuospatial Memory Test-Revised [BVMT-R] (Benedict, 1997).

The BICAMS consensus committee considered two tests to assess information processing speed: the Paced Auditory Serial Addition Test [PASAT] (Gronwall, 1977) and the Symbol Digit Modalities Test [SDMT] (Smith, 1982; Langdon et al., 2012). The two tests have comparable psychometric validity but the Symbol Digit Modalities Test [SDMT] (Smith, 1982) is noted for being better tolerated by subjects with weak computational skills and less irritating than the Paced Auditory Serial Addition Test [PASAT] (Gronwall, 1977) with its demanding response stimuli (Drake et al., 2010). Furthermore, the Symbol Digit Modalities Test [SDMT] (Smith, 1982) has been advocated as a potential single-test screen for MS-related cognitive impairment (Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007).

TREATMENT OF MS-RELATED COGNITIVE IMPAIRMENT

Research investigating pharmacological treatments for cognitive impairment in MS has been disappointing (Krupp et al., 2011). Pharmacologic agents including pemoline, amantadine, ginkgo biloba, and amphetamine have failed to produce consistent

improvement in cognitive function in persons with MS (Geisler et al., 1996; Lovera et al., 2007; Morrow, Kaushik, et al., 2009). Several studies have investigated the effectiveness of acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine) – a class of drugs used to treat cortical cholinergic deficits in dementias such as Alzheimer's Disease (Doraiswamy & Rao, 2004). Based on encouraging, but modest, results of a 24-week randomized clinical trial (n = 69) of daily donepezil dosing (10 mg) on verbal learning and memory, a larger (n = 120) multicenter trial was conducted by the same investigator (Krupp et al., 2004; Krupp et al., 2011). Unfortunately, no statistically significant differences were found in verbal memory or self-reported memory change between the intervention and placebo-control groups (Krupp et al., 2011).

The effectiveness of non-pharmacological therapies to treat cognitive impairment is equivocal, but patients may derive some benefit from treatment (Messinis et al., 2010). Studies investigating the impact of cognitive rehabilitation on attention, memory, and communication skills in persons with MS have been mixed (O'Brien et al., 2008). The studies have had significant methodological weaknesses including dissimilar cognitive outcome measures and small heterogeneous samples making comparisons among studies difficult (Mattioli, Stampatori, Bellomi, et al., 2010). Cognitive rehabilitation programs focus on two approaches: (1) restorative therapy, direct retraining of specific cognitive domains (e.g., attention, memory) which is hypothesized to improve functional abilities through the reorganization of intact neural networks (neuroplasticity) and (2) compensatory therapy, which assists patients learn and practice strategies designed to

work around their cognitive deficits (e.g., using lists, assistive-technology, mnemonics) (Messinis et al., 2010, Pierson & Griffith, 2006).

Computer-assisted cognitive rehabilitation programs show promise in improving and maintaining cognitive function in persons with MS (Mattioli, Stampatori, Zanotti, et al., 2010; Shatil et al., 2010; Stuifbergen et al., 2012). Mattioli, Stampatori, Zanotti, et al. (2010) reported significant ($p < 0.05$) improvement in attention, information processing and executive function after a 3-month long computer-assisted cognitive rehabilitation program. Stuifbergen et al. (2012) took a novel approach by developing a small, in-person group program that combined behavioral and lifestyle adjustments with compensatory strategies and practice playing computer games focused on attention, memory, problem solving and executive function. The 8-week program had significant ($p < 0.05$) group by time interaction effects on the use of compensatory strategies and verbal memory. The program is currently being tested in a multi-site randomized clinical trial with a larger sample (n = 180).

DEPRESSION AND DEPRESSIVE SYMPTOMS IN PERSONS WITH MS

Nearly one in two persons with MS will develop major depression through the course of the disease (Feinstein, 2006). Mood disorders, including major depressive disorder, are associated with higher lifetime prevalence in persons with MS (36%-54%) than in the general population (16.2%) and most other neurologic conditions (Minden et al., 2014). High prevalence rates of depression and depressive symptoms have been reported in samples derived from MS specialty clinics as well as community-residing samples (Chwastiak et al., 2002). Regrettably, while depression in MS prevalent, it is

frequently unrecognized and left untreated (Siegart & Abernethy, 2005). Depressed mood in persons with MS has been attributed to multiple factors including pathologic changes within the central nervous system as well as grief and loss associated with living with a chronic disabling condition (Minden et al., 2014)

Depression is a mood disturbance diagnosed by clinicians using standardized classification systems such as the ICD-10 or DSM-V, while depressive symptoms are signs (e.g., low mood, irritability, worry) expressed verbally or through self-report questionnaires, scales, or checklists (Minden et al., 2014). Depressive symptoms have been associated with poor outcomes similar to those associated with fatigue: reduced quality of life, impaired cognition and treatment adherence (Gulick, 1997; D'Alisa et al., 2006; Mohr et al., 1997). Common confounders of depression in persons with MS include: fatigue, sleep disturbance, changes in appetite, and impaired cognition (Feinstein, 2011a). Lynch, Kroencke & Denney (2001) reported that emotion-centered coping styles, MS-related disability, uncertainty, and hope were independent predictors of depression among 188 patients with MS and explained 40% of the variance in self-reported depression. Major depression and the severity of depressive symptoms have been linked with higher morbidity and mortality (suicide) in patients with MS (Feinstein, 2002). Data suggest that suicide is contemplated by more than one of every four patients with MS and that suicide risk factors include "the presence of major depression, social isolation and alcohol abuse" (Feinstein, 2002; Feinstein, 2011a, p. 1277).

Evidence supporting the effectiveness of pharmacologic and cognitive-behavioral therapies in the treatment of depression in MS has been equivocal (Minden et al., 2014).

The 2011 Cochrane Review by Koch, Glazenborg, Uyttenboogaary, Mostert and De Keyser found only two studies (70 subjects) out of 1217 met all inclusion criteria in their investigation of the efficacy and tolerability of pharmacologic treatments for depression in patients with MS. Data suggested a trend towards efficacy in treating depression in MS compared to placebo using either desipramine (a tricyclic antidepressant) for five weeks or paroxetine (a selective-serotonin reuptake inhibitor) for 12 weeks. Notable adverse effects (nausea and headache with paroxetine, constipation, dry mouth, and hypotension with desipramine), wide disparity in the length of the trials (5 versus 12 weeks), as well as high number of patients lost to follow-up contributed to the authors' decision to forgo conducting a meta-analysis. Cognitive behavioral therapy (CBT) "is used to treat depression by conferring skills to identify and reappraise negative thoughts impacting on feelings and behaviors" (Hind et al., 2014, p. 2). Data from a recent meta-analysis investigating the effect of CBT for the treatment of depression in persons with MS found a medium treatment effect (0.56 SD, SMD -0.61, 95% -0.96 to -0.26, $p = 0.0006$) at the end of treatment for individual, group or computerized cognitive behavioral therapy (Hind et al., 2014).

FATIGUE IN PERSONS WITH MS

Fatigue related to MS is the most frequently reported and arguably among the most disabling symptoms of the disease. The majority of persons with MS experience significant fatigue on a daily basis (Fisk, Pontefract, et al., 1994). In a nationally representative sample of over 4000 individuals with MS, more respondents cited fatigue

(83%) as a current symptom than difficulties with ambulation (67%), spasticity (63%) or cognitive problems (56%) (Minden et al., 2006).

Fatigue is a subjective, multidimensional phenomenon that is challenging to define, and is particularly vulnerable to retrospective bias (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009). Fatigue has been postulated to have primary mechanisms related to MS pathology (demyelination and axonal loss) as well as secondary mechanisms attributed to disturbed sleep, pain, and anxiety (Kos, Kerckhofs, Nagels, D'Hooghe, & Ilsbroukx, 2008). The sedating effects of medications used to treat these MS comorbidities may also potentiate fatigue (Kos et al., 2008). Exposure to heat or increased body temperature tends to exacerbate fatigue in persons with MS, which is not seen in other neurologic conditions (Kos et al., 2008).

Fatigue also has underlying psychological mechanisms related to mood, cognition and personality (Bol et al., 2009). There is considerable overlap between symptoms of fatigue and depression - lack of energy, tiredness, lack of motivation (Bol et al., 2009; Kos et al., 2008). Impaired sleep, disease severity and depression have been identified as independent predictors of fatigue in persons with MS with sleep being the strongest predictor ($\beta = .36$, $p < .001$) interacting with depression ($\beta = .31$, $p < .01$) (Strober & Arnett, 2005). There is some evidence that certain personality traits [negative affectivity (neuroticism), high conscientiousness and low extraversion] may play a role in fatigue experience in persons with MS (Bol et al., 2009).

While the causes of fatigue in MS are not clearly understood, its consequences are significant. Fatigue negatively impacts social, emotional, cognitive and physical

functioning in those with MS and is related to lower health-related quality of life and unemployment (Krupp, 2003; Rietberg, van Wegen, Uitdehaag, & Kwakkel, 2011). Despite MS-related fatigue being so prevalent, its pathophysiology is not well understood and therapeutic regimens lack robust effects (Kluger, Krupp, & Enoka, 2013). Multidisciplinary treatments suggested to manage MS-related fatigue include "a combination of aerobic exercise, a rehabilitation program, body cooling, energy conservation strategies and psychological and dietary interventions" (Kos et al., 2008, p. 96). Pharmacological therapy (amantadine, modafinil) has been suggested in clinical practice guidelines, yet a recent meta-analysis reported a non-significant pooled effect size of 0.07 (95% CI: -0.22 – 0.37, $p = 0.63$) for the effect of pharmacological interventions using amantadine and modafinil on fatigue in persons with MS (Kesselring & Beer, 2005; Asano & Finlayson, 2014). The same meta-analysis reported significant, moderate pooled effects for exercise and educational interventions on fatigue in persons with MS (0.57, 95% CI: 0.10 – 1.04, $p = 0.02$ and 0.54, 95% CI: 0.30 – 0.77, $p < .001$ respectively), respectively (Asano & Finlayson, 2014).

INTERRELATIONSHIPS BETWEEN COGNITIVE IMPAIRMENT, DEPRESSION, AND FATIGUE IN PERSONS WITH MS

Depression and fatigue are influential factors related to cognitive function in MS but the nature of the interrelationships is ambiguous. Features of MS-related depression and fatigue (e.g., attention, lethargy, poor concentration) confound performance on cognitive assessments and raise concern about construct validity (Bol et al., 2009; Langdon, 2011). Distinguishing the discrete contributions depression and fatigue may

have on cognitive impairment is difficult given substantial intra-individual differences and shared construct characteristics.

Methodological shortcomings have been identified among early studies, which found no relationship between depression and cognitive impairment in persons with MS (Feinstein, 2006). More recent and better designed studies impart cautious support to relationships existing between moderate to severe depression and impairments in cognitive capacity (attention), processing speed, working memory, and executive function (Arnett, Higginson, Voss, Bender, et al., 1999; Arnett, Higginson, Voss, Wright, et al., 1999; Demaree, Gaudina, & DeLuca, 2003). While cognitive limitations experienced by persons with MS may contribute to depressive symptoms, Feinstein (2006) reports that depression may potentiate cognitive impairment by depleting attentional and cognitive capacity, which in turn is hypothesized to impede memory and executive functions in a hierarchical fashion. It is currently unknown whether treatment of depression will result in improved cognition, justifying further investigation (Feinstein, 2006; Siegert & Abernethy, 2005).

The relationship between fatigue and cognitive function is even more equivocal. Difficulty in quantifying fatigue, a subjective and complex construct, has impeded research related to fatigue characteristics, mechanisms and treatment (Chadhuri & Behan, 2004; Pierson & Griffith, 2006). Medications commonly used to manage MS symptoms (e.g., spasticity, neurogenic pain, depression) may exacerbate fatigue and impair cognitive function further confounding the relationship (Patti, 2009; Pierson & Griffith, 2006). Studies investigating fatigue and cognitive impairment have yielded

inconsistent results. A number of studies have reported significant associations between fatigue and cognitive function, specifically processing speed ($r = -0.35$, $p < .05$), attention ($\beta = 0.298$, $p = 0.014$), recognition reaction time ($\beta = 0.559$, $p < .05$), and accuracy ($\beta = -0.405$, $p < .05$) (Andreasen, Spliid, Andersen, & Jakobsen, 2010; Holtzer & Foley, 2009; Weinges-Evers et al., 2010). Other studies have reported null relationships between fatigue and cognition (Bailey, Channon, & Beaumont, 2007; Krupp & Elkins, 2000; Parmenter, Denney, & Lynch, 2003).

In summary, cognitive impairment, fatigue and depression are common, confounding, debilitating symptoms of MS. Methodological shortcomings such as small sample size and selection bias have plagued studies examining the relationship between cognition and depression as well as between cognition and fatigue. Additionally, fatigue is an abstract concept that is uniquely subjective, difficult to define and quantify adequately. Strategies to manage depression, fatigue and cognitive impairment in persons with MS (e.g., pharmacotherapy, cognitive behavioral therapy) offer mixed effects.

PHYSICAL ACTIVITY

Physical activity has been posited as a therapeutic intervention to minimize cognitive impairment, depression, depressive symptoms and fatigue related to MS (Bol et al., 2009; Ensari, Motl, & Pilutti, 2014; Feinstein, 2011b; Motl, Sandroff, & Benedict, 2011; Pilutti et al., 2013). Physical activity is defined as "bodily movement that is produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting energy expenditure" (Pescatello, 2014, p. 2).

Physical activity is an umbrella concept encompassing all forms of muscle movement. Therefore, it is often categorized by the context in which it occurs: leisure-time, occupational, sport, transportation and household (Caspersen et al., 1985). Another method of classifying physical activity is based on physiological outcomes: aerobic, muscle strengthening, bone strengthening, and stretching (USDHHS, 2011). Aerobic activity is promoted for improving heart and lung function; muscle strengthening activities for stimulating muscle power, strength, and endurance; bone strengthening activities for fostering bone growth and reducing the risk for developing osteoporosis; and stretching activities for improving or maintaining joint range of motion and flexibility which may reduce the risk of falling (Physical Activity Guidelines Advisory Committee, 2008).

Exercise is a subset of physical activity that is structured, planned, repetitive, and goal directed (Caspersen et al., 1985). Exercise is focused; it has specific aims such as improved health, physical performance or physical fitness (Bouchard, Blair, & Haskell, 2012). Common forms of exercise include aerobic/endurance training (e.g., walking, cycling, rowing), which is aimed at maintaining or improving heart and lung function and strength/resistance training (lifting weights) that focuses on preserving or increasing muscle mass and strength.

Physical fitness is defined as "a set of attributes which allow individuals to perform physical activity with greater ease" (Porcari & Foster, 2010, p. 68). Important components of health-related physical fitness include: cardiovascular endurance, body composition, muscular strength and endurance, and flexibility (Bouchard et al., 2012;

Pate, 1988). While physical fitness and physical activity are related, health-related benefits of physical activity may be realized despite any measurable improvements in fitness status (Pescatello, 2014; Physical Activity Guidelines Advisory Committee, 2008).

Regular physical activity has been related to better quality of life, health status, and longevity in adults regardless of gender, age, ethnicity and race (Bouchard, Blair, & Haskell, 2012; Chodzko-Zajko et al., 2009; Physical Activity Guidelines Advisory Committee, 2008). Despite substantial health benefits, data from the 2010 Behavioral Risk Factor Surveillance System indicates that one in four American adults do not report engaging in any leisure-time physical activity (Moore, Harris, Carlson, Kruger, & Fulton, 2012). Leisure-time physical activities are self-selected discretionary activities, such as taking the stairs rather than the elevator, which increase the total daily energy expenditure (Bouchard et al., 2012). The World Health Organization (2010) has identified physical inactivity as the fourth leading risk factor for mortality worldwide. Physical inactivity substantially increases the risk for developing chronic diseases, premature mortality, and the number of years lived with disability (USDHHS, 2008; US Burden of Disease Collaborators, 2013).

While the rates of physical activity among adults are low, rates among older adults and persons with living with a disability are lower still. This presents a substantial problem as the number of older adults age 65 years and older is expected to exceed 70 million individuals (19% of the total population) by the year 2030 (Administration on Aging, 2013). Only 1 in 4 (27%) adults age 65-74 reports participating in leisure-time

physical activity (Schoenborn, Vickerie, & Powell-Griner, 2006). Physical activity rates continue to fall as adults enter their 7th and 8th decade of life; only 18% of 75-84 year olds and 8.2% of adults 85 years and older report any leisure-time physical activity (Schoenborn et al., 2006). Lack of physical activity is twice as likely among the 50 million Americans who report living with a disability than those with no disability and nearly 10.1 million adults with a disability do not get any aerobic physical activity (CDC, 2007; CDC, 2013; CDC, 2014).

To address the increasingly low rate of physical activity and high prevalence of chronic disease and disability in the United States, the Physical Activity Guidelines Advisory Committee published the Physical Activity Guidelines for Americans in 2008. The committee's extensive review of the literature resulted in recommendation of "at least 150 minutes a week of moderate-intensity, or 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity" for adults, older adults, and adults with disabilities (USDHHS, 2008, p. 22). Individuals with disabilities are advised to follow these recommendations as their condition allows and for those "who are unable to meet these guidelines, they should engage in regular physical activity according to their abilities and should avoid physical inactivity" (USDHHS, 2008, p. 43).

Meta-analytic evidence indicates that persons with MS are less physically active than adults without chronic disabling conditions (Motl, McAuley, & Snook, 2005). Cross-sectional data from a nationally representative sample of persons with MS suggests that up to 70% of adults with MS are inactive (Marrie et al., 2009). Additionally, there is

substantial evidence of diminished fitness (i.e., aerobic capacity, muscle strength, and endurance) among persons with MS (Döring et al., 2012). Physical inactivity and sedentary lifestyles place persons with MS at increased risk of developing cardiovascular disease, diabetes, and obesity in addition to secondary conditions related to MS (e.g., bladder/bowel problems, pressure sores, osteoporosis) (Dalgas, Stenager, & Ingemann-Hansen, 2008). Advancing age and progressive disability contribute to sedentary behavior and further challenges health maintenance in persons with MS. A cyclic pattern of increased inactivity, depression, and fatigue may result in further deconditioning and disablement (MacAllister & Krupp, 2005). Historically, physical activity was thought to increase the risk of MS exacerbations; this presumed association has not been supported by the literature (Pilutti, Platta, et al., 2014; Rietberg et al., 2011; Tallner et al., 2012). In fact, a substantial body of research exists supporting the positive effects physical activity has on persons with MS including improvements in mood, muscle function, and mobility (Latimer-Cheung, Pilutti, et al., 2013; Rietberg et al., 2011; White & Dressendorfer, 2004).

Physical activity guidelines specifically designed for persons with MS have been developed and are available online through The Canadian Society for Exercise Physiology (Ginis & Hicks, 2007). More recently, a consensus panel of experts developed physical activity guidelines for adults with MS using a rigorous process based on an extensive systematic review of the literature (Latimer-Cheung, Martin Ginis, et al., 2013; Latimer-Cheung, Pilutti, et al., 2013). The guidelines promote fitness benefits for adults with MS who have mild to moderate disability through "30 minutes of moderate

intensity aerobic activity 2 times per week and strength training exercises for major muscle groups 2 times per week" (Latimer-Cheung, Martin Ginis, et al., 2013, p. 1829).

In summary, many individuals with MS lead sedentary lifestyles and are less physically active than the general population of whom, according to the data from the 2015 National Health Interview Survey, only 20.9% of adults 18 years and older meet the 2008 guidelines for both aerobic activity and muscle strengthening based on leisure-time activity (USDHHS, 2016). Physical inactivity contributes to negative health outcomes and secondary conditions in persons with MS. Increasing physical activity in persons with MS has been recognized as a feasible strategy for maintaining function, promoting health and improving quality of life through its positive effects on physical, mental and psychosocial function (Stuifbergen & Roberts, 1997; Physical Activity Guidelines Advisory Committee, 2008; Motl & Gosney, 2008; Rietberg, Brooks, Uitdehaag, & Kwakkel, 2004). Physical activity guidelines to promote health and wellness for persons with MS have recently been developed and published (Latimer-Cheung, Martin Ginis, et al., 2013).

INTERVENTIONS DESIGNED TO INCREASE PHYSICAL ACTIVITY IN PERSONS WITH MS

There is great variation among approaches used in intervention studies designed to increase physical activity in persons with MS: directly supervised exercise (Oken et al., 2004; Petajan et al., 1996; Velikonja. Curic, Ozura, & Jazbec, 2010), internet-delivered health promotion (Pilutti, Dlugonski, Sandroff, Klaren & Motl, 2014; Sandroff et al., 2014), group health promotion (Stuifbergen et al., 2003), group efficacy-enhancement (McAuley et al., 2007) and telephone-delivered counseling (Bombardier et

al., 2008). Dixon-Ibarra et al. (2014) claim that the science of physical activity research in persons with MS is "still in its infancy" (p. 155) due to a limited number of studies focused on changing physical activity behavior in persons with MS.

The establishment of physical activity guidelines is essential to the development of effective programs (Dixon-Ibarra et al., 2014). Only recently has the effectiveness of physical activity interventions on critical outcomes been quantified to develop physical guidelines for persons with MS (Latimer-Cheung, Martin Ginis et al., 2013). The authors' concluded after reviewing 54 studies that physical activity interventions are effective for improving muscular strength and aerobic capacity in persons with mild to moderate disability related to MS (Latimer-Cheung, Pilutti et al., 2013). While promising, they concluded that there was insufficient evidence to support the effectiveness of physical activity interventions to improve mobility, fatigue or health-related quality of life outcomes in persons with MS (Latimer-Cheung, Pilutti et al., 2013). The guidelines define the target population (persons with MS who have mild to moderate disability), intensity (moderate), aerobic training session duration (30 minutes) and frequency (2 times per week aerobic and resistance training), yet fail to provide guidance on the optimal program duration (Latimer-Cheung, Martin Ginis et al., 2013).

An earlier Cochrane Review examined nine randomized controlled trials (RCTs) finding support for exercise therapy over no exercise therapy for improving muscle power, mobility and exercise tolerance but not fatigue among persons with MS (Rietberg, et al., 2004). The authors recommended that a core set of outcome measures be developed and that future studies clearly define the exercise dose (e.g., type, intensity,

session length, frequency and program duration). These recommendations have yet to be satisfied; perhaps due to the great variability MS has on each individual's physical (e.g., balance, strength) and cognitive functional systems. Of 11 RCTs reviewed by Asano, Dawes, Arafah, Moriello, and Mayo (2009), five of the studies did not present information on exercise intensity and over 31 different target outcomes were identified (i.e., aerobic capacity, muscle strength, fatigue, health-related quality of life, mobility). Similar heterogeneity was described by Latimer-Cheung, Pilutti, et al. (2013) among the 24 RCT studies they reviewed that included numerous physical activity interventions: aerobic exercise, resistance training, combination aerobic and resistance training, robotic-assisted treadmill training, yoga, swimming, as well as stability and plyometric exercises. Among the 28 RCTs included in both systematic reviews, intervention sessions ranged in length from 25 to 90 minutes (mean = 46.3 $\pm$ 17.5), met from 1 to 7 times per week (mean = 3.1 $\pm$ 1.5), and the programs lasted from 4 to 26 weeks (mean = 10.7 $\pm$ 6.7). The moderating effects of exercise type, intensity, session length, frequency or program duration were not reported in any of the reviews (Asano et al., 2009; Latimer-Cheung, Pilutti et al., 2013; Rietberg et al., 2004). The outcomes reported by Latimer-Cheung, Pilutti et al. (2013) were "reported immediately after the intervention, thus precluding the potential to determine the long-term effects of exercise training" (p. 1825). Therefore, the optimal dose of physical activity intervention (exercise type, intensity, session length, frequency or program duration) has yet to be determined for studies investigating the effects of physical activity on MS-specific outcomes such as cognitive impairment, fatigue and depressive symptoms.

Effects of Physical Activity Interventions on MS-Related Symptoms

There has been an emphasis on research exploring potential relationships between physical activity behavior and MS-related health outcomes including depression, fatigue and cognitive function (Dixon-Ibarra et al., 2014). Inquiry into the effectiveness of physical activity behavior change interventions on MS-related symptoms is less common. The following reviews the literature examining the effects of physical activity on fatigue, depression, depressive symptoms, and cognitive function.

Effect of physical activity on depression, depressive symptoms, and fatigue in persons with MS

Evidence of the effectiveness of physical activity interventions to ameliorate depressive symptoms or fatigue in MS has been unclear based on reviews of the literature (Andreasen, Stenager, & Dalgas, 2011; Feinstein, Rector, & Motl, 2013). Two recent meta-analyses addressed this paucity of evidence in the MS literature (Ensari et al., 2014; Pilutti et al., 2013). Ensari et al. (2014) found physical activity interventions had a small, statistically significant effect on improving depressive symptoms (Hedge's $g = 0.36$, $SE = 0.09$, 95% CI = 0.18 – 0.54, $z = 3.92$, $p < .001$). Correspondingly, Pilutti et al. (2013) reported that exercise training had a significant, small-to-moderate effect on reducing fatigue (Cohen's $d = 0.45$, $SE = 0.12$, 95% CI = 0.22 – 0.68, $z = 3.88$, $p \leq .001$).

Both meta-analyses used the Physiotherapy Evidence Database (PEDro) scale to evaluate the quality of the studies included in their analysis (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). The majority of the studies were of high quality (69% in Ensari et al., 2014 and 76% in Pilutti et al., 2013). The authors of both meta-analyses noted wide variation among the exercise interventions employed (e.g., mode, duration,

intensity, individual versus group), instruments used to measure depressive symptoms/fatigue, identification of depressive symptoms/fatigue as secondary rather than primary outcomes, and potential ceiling effect since depressive symptoms/fatigue were not screened for or used as inclusion criteria. In summary, while the effect sizes were small, the findings of these meta-analyses support the utility of physical activity to improve depressive symptoms and fatigue in persons with MS.

EFFECTS OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTION.

In older adults

Robust effects derived from five meta-analyses evaluating the effectiveness of physical activity interventions on cognitive function in older adults provide the rationale for the proposed study (see Appendix H; Table 1). Samples in the studies included in the meta-analyses were comprised of healthy older adults, adults with mild cognitive impairment and dementia, as well as adults with chronic conditions (i.e., chronic obstructive pulmonary disease, fibromyalgia, and MS). Smith et al. (2010) included three samples involving younger adults among the 29 studies they analyzed. Of note, only the Colcombe and Kramer (2003) meta-analysis failed to evaluate the quality of the studies included in their analysis, which may account for the much larger effect sizes reported in this early meta-analysis.

Effects pooled from physical activity interventions were significant for several cognitive outcomes including: general cognitive function, attention and processing speed, executive function, memory, and verbal fluency (Colcombe & Kramer, 2003; Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013; Heyn et al., 2004; Hinden & Zelinski,

2012; Smith et al., 2010). Moderator analyses suggest that combined resistance-aerobic programs were more effective than aerobic training alone for all cognitive outcomes in Colcombe and Kramer (2003) and for attention and processing speed in Smith et al. (2010). Additionally, Colcombe and Kramer (2003) reported that program and session duration were significant moderating variables with longer programs (six-months or longer) and moderate session length (31 – 45 minutes) resulting in larger effect sizes.

IN PERSONS WITH MS

Studies investigating physical activity and cognition in persons with MS have proliferated over the past decade. Much of the interest in this phenomenon can be attributed to the robust effect physical activity has on cognition in older adults previously discussed. Sixteen studies exploring physical activity and cognition in persons with MS were found in the literature; six are observational studies, three are quasi-experimental, and seven are experimental (see Appendix H; Tables 2-4).

The six descriptive studies reported several significant associations between measures of physical activity and measures of cognitive function (information processing speed, attention, memory, and executive function), brain structures and brain functions. Physical activity was measured using data collected by accelerometers (Motl, Gappmaier, et al., 2011; Prakash et al., 2011; Prakash, Snook, Kramer, & Motl, 2010). Use of accelerometers to quantify physical activity has been validated in ambulatory persons with MS (Gosney, Scott, Snook, & Motl, 2007; Motl, McAuley, Snook, & Scott, 2006). Cardiorespiratory fitness, measured as peak oxygen consumption, was used as a proxy for physical activity in three of the studies (Prakash et al., 2007; Prakash, Snook, Motl, &

Kramer, 2010; Beier, Bombardier, Hartoonian, Motl, & Kraft, 2014). Concern has been raised that measures of physical fitness, which are physiologic attributes related to physical activity, may not be directly modifiable by change in behavior and as such may not reflect the relationship between physical activity behavior and cognitive outcomes (Motl, Gappmaier, et al., 2011; Prakash, Snook, Kramer, & Motl, 2010).

The type of MS varied among the studies; three studies included individuals with any form of MS documented by a physician while the others included only persons with the most common form of the disease, relapsing-remitting MS (Multiple Sclerosis International Federation, 2013). The study sample sizes ranged from 21 to 88 persons and consisted mainly of females. The Expanded Disability Status Scale (EDSS) was employed in all but one study to describe the impact of MS on the participants' neurologic status (Kurtzke, 1983). The EDSS measures neurologic impairment in MS based on assessment of eight functional domains: visual (optic), brain stem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral, and ambulation.

There was great variation in the type of cognitive function, brain structure and brain function variables explored as well as in the methods used to measure the variables in the studies reviewed. Cognitive function variables focused on areas of cognition commonly impaired among persons with MS; specifically processing speed, attention, and executive function. Several clinical instruments were employed to assess cognitive function. The most frequently used instruments were the Paced Auditory Serial Addition Test (Gronwall, 1977), which measures attention, processing speed, and working memory (Tombaugh, 2006) and the Symbol Digit Modalities Test, a test of complex scanning and

visual tracking (Smith, 1982). One study used the Perceived Deficits Questionnaire, a self-report instrument to assess cognitive function (Sullivan, Edgley, & Dehoux, 1990). MRI was used to assess brain structures and function in three studies (Prakash et al., 2007; Prakash et al., 2011; Prakash, Snook, Kramer, & Motl, 2010).

Findings among the descriptive studies included significant relationships between physical activity and self-reported cognitive function, processing speed, and hippocampal connectivity (Motl, Gappmaier, et al., 2011; Prakash, Snook, Kramer, & Motl, 2010; Prakash et al., 2011). Cardiovascular fitness was significantly associated with information processing speed, attention, working memory, executive function, cerebrovascular function, gray matter volume and fractional anisotropy values (Prakash et al., 2007; Prakash, Snook, Motl, & Kramer, 2010; Beier et al., 2014). In summary, findings from these cross-sectional studies provide preliminary evidence to support experimental investigation into the causal relationship and temporal sequencing of physical activity and cognition in persons with MS.

Three quasi-experimental studies (one group, pretest/posttest) examining the effects of physical activity on cognition were included in the review. Samples ranged in size from 10 to 33 and were composed mainly of women. One study included persons with progressive MS and a wide range of disability with EDSS scores from 1.5 (independent ambulation) to 8.0 (limited to bed, chair or passive use of wheelchair) while the other two included participants with confirmed MS of any type and EDSS scores from 1.0 (little disability fully ambulatory) to 6.5 (moderate disability, able to walk 25 feet with or without an assistive device) (Filipi et al., 2010; Freeman & Allison, 2004;

Kurtzke, 1983; Roehrs & Karst, 2004). The interventions employed varied in type (floor, aquatic, resistance), frequency (1 or 2 days per week) and duration (10 to 24 weeks). The level of exercise intensity was not defined for any of the studies. Significant findings related to cognition were limited to one study, which reported improvement in attention and memory measured using the Paced Auditory Serial Addition Test (Filipi et al., 2010; Gronwall, 1977).

Experimental studies investigating the effects of physical activity on cognition, including cognitive function related to fatigue, were reviewed (see Appendix H; Table 4). The studies included one randomized prospective design (Velikonja et al., 2010), and six reports of five RCTs (Oken et al., 2004; Romberg, Virtanen, & Ruutiainen, 2005; Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012; Briken et al., 2014; Pilutti, Dlugonski, et al., 2014; Sandroff et al., 2014). Velikonja et al. (2010) reported a statistically significant effect ($p < .01$) of a ten-week yoga program on selective attention and cognitive function related to fatigue but this study had concerning quality issues including small sample size, unstated assignment to treatment arms, and no report of the participants' gender. Oken et al. (2004) and Romberg et al. (2005) reported no significant findings among the cognitive function outcomes measured after yoga, stationary cycling, or a combined program of inpatient rehabilitation for 3 weeks followed by 23 weeks of an independent home-based program of resistance training.

In summary, limited research exists which examines the effects of physical activity on cognition in persons with MS and what research does exist is predominantly cross-sectional or single group pretest/posttest design. Reports of more rigorous studies

are increasing. Five reports of four RCTs were found that measured cognitive function outcomes after a physical activity intervention in persons with MS. Notably, only three of the four experimental design studies identified cognitive function as a primary outcome (Oken et al., 2004; Sandroff et al., 2014; Velikonja et al., 2010). No significant improvements in cognitive function were found in the Oken et al. (2004) and Romberg et al. (2005) studies. Kargarfard et al. (2012) found a significant group by time interaction for an eight-week supervised aquatic program on the cognitive subscale of the Modified Fatigue Impact Scale.

Exercise components used in the experimental studies varied a great deal. Quantifying the volume of exercise required to elicit an effect in the studies reviewed was not feasible due to great variability among types (aquatic exercise, yoga, sports climbing, and combination resistance/aerobic endurance training), methods of delivery (group, home, and internet) and length (eight weeks to six months) of physical activity interventions implemented. Additionally, there was considerable variation among the instruments used to assess cognitive function since no single test exists to adequately assess cognitive impairment (Benedict, 2011). The studies may have been underpowered as only one reported conducting a power analysis to determine adequate sample size (Sandroff et al., 2014). Lastly, intention to treat analysis, which avoids artifact due to non-random attrition of participants, was used in only two studies (Kargarfard et al., 2012; Sandroff et al., 2014).

The gaps in knowledge and the dearth of treatments available to manage cognitive impairment in persons with MS demand an innovative approach. Research of physical

activity in persons with MS has established its therapeutic value as an effective, well tolerated therapy for impaired physical functioning, depressive symptoms, fatigue and quality of life (Döring et al., 2012; Ensari et al., 2014; Motl & Gosney, 2008; Motl & Pilutti, 2012; Pilutti et al., 2013); the next step is to add to the emerging body of research by determining the feasibility and effectiveness of a methodologically rigorous physical activity program to promote cognitive functioning in persons with MS.

SUMMARY

This chapter reviewed the literature related to the prevalence, impact and treatment of cognitive impairment, depression and fatigue in persons with MS. Based on studies involving persons with MS, healthy older adults, older adults with cognitive impairment, and persons with chronic conditions, physical activity is advanced as a viable self-management approach for addressing MS-related cognitive impairment, depression, and fatigue. Research studies have shown that physical activity is a safe and effective therapeutic option for maintaining functional abilities, decreasing the severity of MS-related symptoms and promoting quality of life.

This study aspires to decrease the impact and burden of cognitive impairment and resultant day-to-day functional limitations individuals with MS, their families, and society experience. This study explored the feasibility and effectiveness of the Physically Active Lifestyle in MS (PALMS) intervention – a tailored, small group, moderate intensity physical activity intervention for this population. The information gleaned from this study can be integrated into clinical practice in numerous healthcare disciplines

including: nursing, neurology, neuropsychology, physical therapy, occupational therapy, and rehabilitative medicine.

Chapter 3: Methods

This chapter details the study design, setting, and sample characteristics, as well as the procedures used for the protection of human subjects. Furthermore, data collection methods, instrumentation, intervention protocol and data analyses are described.

DESIGN

This study employed a quasi-experimental design conducted in a community setting with a convenience sample of 16 adults with MS prescreened for cognitive problems and physical inactivity. The purpose of the study was to determine the feasibility and effects of a physical activity intervention on the primary outcomes of clinical cognitive function and neurocognitive function in everyday life in addition to the secondary outcomes of exercise self-efficacy, physical activity, depressive symptoms and fatigue. Data were collected at baseline, 3-months and 6-months (post-intervention) using self-report measures, an objective measure of physical activity, and neuropsychological tests. An attention-control group was selected for this study as this form of comparison group allows for equal exposure (contact time) and attention over the six-month intervention period of this trial of a non-pharmacologic intervention.

STUDY PROCEDURES

Participant recruitment

Participants were recruited from communities in and around metropolitan Austin, Texas. Austin is the state capital and the center of a metropolitan area of approximately 1 million people. According to the 2011 US Census Bureau estimates, the population is

approximately 50% White/non Hispanic, 34% Hispanic, 9% Black, and 6% Asian and 2% other. The Lone Star Chapter of the National MS Society serves more than 1400 Persons with MS in Travis County. The investigator's prior work on the dissertation chair's studies has allowed her to build strong connections with this population and service providers throughout the community.

Participants were recruited in a variety of ways including referrals from local neurologists, advanced practice nurses at a MS-specific neurology clinic with approximately 1,200 MS patients (see Appendix C), 10 presentations to MS support groups, and "word of mouth." Recruitment materials were distributed instructing potential participants to email the principal investigator or call the dissertation chair's research office toll-free number for additional information about the study.

Recruitment began upon receipt of IRB approval on November 25, 2014 and was ongoing to establish small groups of subjects. Based on the literature and prior experience in previous studies, small group cohorts (2 to 4 persons) allow for optimal interaction among subjects to enhance self-efficacy through vicarious experience and modeling (Bandura, 1997). Individuals were assigned to either the intervention (strength and aerobic exercise program) or attention-control (relaxation and stretching) group after successful completion of baseline data collection. The first nine participants were randomly assigned using a computer-generated list of random numbers. Randomization assignment was recorded on a letter and sealed in an opaque envelope; following the completion of baseline testing the investigator opened the next envelope in the sequence and assigned the participant to either the intervention or attention-control group. After

nine months of continuous recruiting efforts (including 10 presentations to three different MS support groups in the Austin area) nine individuals had been successfully enrolled in the study, seven had been randomly assigned to the attention-control group and two into the intervention group. The random assignment of the tenth participant on September 13, 2015 (ten months into recruitment) was to the attention-control group. The PI immediately consulted the dissertation chair by phone while the participant was undergoing baseline neuropsychological testing. The decision was made to assign the tenth participant to the intervention group since the randomization protocol for the study had resulted in a great size disparity between the intervention and attention-control groups. The dissertation committee and the NIH program official were consulted on October 6, 2015 and all agreed that the design of the study would be changed to quasi-experimental in order to have sufficient data about the primary aim of this study, its feasibility. The next four participants were assigned to the intervention group. Thereafter, participants were assigned in alternating fashion to the intervention and attention-control groups. In addition, a large number (14) of those expressing interest in the study had been excluded solely because they engaged in low-intensity lifestyle or transportation-related physical activity (e.g., walking their dog, biking a short distance to work). The PI and the dissertation chair made the decision to change the definition of physical inactivity in the inclusion criteria by replacing “regular physical activity” with “structured exercise” after consultation with exercise physiology content expert and committee member Dr. Robert Motl on October 5, 2015. The Institutional Review board at The University of Texas at Austin approved the above changes to the study on October 8, 2015.

Sample

The sample for this study consisted of 16 adults with physician-diagnosed MS living in the Austin metropolitan area who met screening criteria for cognitive problems and physical inactivity. The goal of the study was to determine the feasibility of the intervention protocol and to provide estimates of effect size for future studies. Using G*Power 3, a 2x3 repeated measures ANOVA within and between design, small to medium effect size (ES f = .175), alpha = .05, and power = .80 computed a total sample size of 26 (Faul, Erdfelder, Lang, & Buchner, 2007). Since there are no similar studies with persons with MS, the small to medium effect size estimate was based on two meta-analyses of aerobic exercise interventions on neurocognitive performance in older adults and adults over age 18 (Colcombe & Kramer, 2003; Smith et al., 2010). Allowing for a 10% attrition rate (based on the dissertation chair's 5-month long cognitive intervention study R21NR011076), 30 persons with MS (15 per group) were to be recruited to participate in the study.

To participate, subjects had to be diagnosed with MS, age 21 to 60, and capable of understanding and complying with the study protocol. Participants also needed to be able to read and write in English and be ambulatory with minimal assistance as objective physical activity measurement devices have only been validated with individuals who walk with or without a cane, but not a walker, wheelchair or scooter (Motl, McAuley, Snook, & Scott, 2006). All participants had a diagnosis of clinically definite MS and written approval to participate in the physical activity program documented by their healthcare provider.

Participants had stable disease at the time of entry into the study (relapse free for at least 90 days), reported being physically inactive, defined as not engaging in structured exercise (30 minutes accumulated each day) on more than 2 days per week during the previous 6 months, score 55 or less on the Symbol Digit Modalities Test (SDMT) – a test of complex scanning and visual tracking (Smith, 1982) considered the standard for effective cognitive impairment screening in the clinical setting for persons with MS (Parmenter et al., 2007) and be willing to participate in a 6-month study involving physical activity and data collection. One participant who scored 56 on the SDMT was included in the study after consultation with the dissertation chair and referring to the SDMT testing manual that states:

> Given the variances and reliabilities reported in this manual, standard error of measurement (*SEM*) estimates of between 2.8 and 5.4 points indicate that *any* score within 6 to 11 points (depending on the sample and administration procedure) of a specific cutoff value needs to be carefully interpreted and verified against other evidence relevant to a particular case. (Smith, 1982, p. 3)

The sample included males, females, Whites, African-Americans, Hispanic and non-Hispanic subjects. Subjects were excluded if they were pregnant or planned to be, had cardiovascular or respiratory disease, other medical causes of dementia (e.g., stroke, Parkinson's disease) or other neurological disorders that may impact cognition or emotions, evidence of major psychiatric disorder, or if they had major functional limitations that precluded them from participating in the study. Evidence of exclusion criteria included self-report by the participant or inference by failure of the healthcare

provider to authorize participation in the study.

Intervention Protocol

The investigator used a script and the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (see Appendix D) to phone-screen potential participants for inclusion/exclusion criteria and to explain the study procedures and requirements (Jamnik et al., 2011). Informants who responded yes to more than one of the follow-up questions in Section 2 - Chronic Medical Conditions of the PAR-Q+ were excluded from participating in the study. Based on the phone screen eligibility and responses to the PAR-Q+, potential subjects were invited to an in-person meeting (at a location, date, and time selected by the subject) to review the study requirements, sign the informed consent and undergo a brief (5 minute) cognitive function screen using the Symbol Digit Modality Test [SDMT] (Smith, 1982), which has been proposed as a promising screening test for cognitive impairment in persons with MS (Parmenter el al., 2007). Participants scoring 55 or less were eligible to participate in the study. Those eligible were asked to provide the name and address of their healthcare provider to 1) verify their MS diagnosis and 2) authorize medical clearance to participate in a physical activity program (see Appendix D). The investigator and participant signed and dated the two forms, which the investigator faxed or delivered in person, along with a cover letter explaining the study, to the healthcare provider. The demographic information sheet, baseline questionnaire, accelerometer and accelerometer log were given to the participant at the meeting. Participants were instructed to complete the survey forms and to wear the accelerometer for seven days during waking hours on their non-dominant hip/waist. At the end of the

seven-day period, the investigator picked up the demographic information sheet, baseline questionnaire, accelerometer, and accelerometer log at a mutually agreed upon location and time convenient for the participant. Neurocognitive testing with a trained research assistant was scheduled upon receipt of the two signed and dated healthcare provider forms. The date, time and location of the first program session (intervention or attention-control) was determined after the neurocognitive testing was complete and baseline materials had been returned.

Participants assigned to the intervention group met twice a week with the investigator (an ACSM/NCHPAD Certified Inclusive Fitness Trainer) for 60 minutes of supervised aerobic physical activity for six months at one of six YMCA of Austin locations. The methodological factors - intervention length (six-months) and session length (60 minutes) - were derived from the meta-analysis by Colcombe & Kramer (2003) that examined the magnitude of effects of physical activity interventions on cognitive function in older adults and the Canadian Physical Activity Guidelines for Persons with MS (Canadian Society for Exercise Physiology, 2013). Each participant underwent a baseline exercise assessment and had an individualized progressive program of exercise based on the assessment and baseline physical activity measures (i.e., Godin Leisure-Time Exercise Questionnaire, accelerometer data). The supervised program consisted of a five-minute dynamic warm-up, up to 30 minutes of aerobic exercise (walking on a treadmill, riding a stationary bike, using an elliptical trainer, or recumbent elliptical trainer) and twenty minutes of strength training, followed by a five-minute cool down with stretching.

To assess and monitor the level of exercise intensity, participants wore a Polar® heart rate monitor aiming for 40 – 60% of maximum heart range using the Tanaka, Monahan, & Seals (2001) formula: 208 – (0.7 x Age) and verbalized rating of perceived exertion between 3 (moderate) and 7 (very strong) using the 10-point Borg Scale (Borg, 1998; Morrison et al., 2008). Heart rate and rating of perceived exertion were recorded every 10 minutes. Participants were encouraged to exercise on their own at least three additional days a week and to document their PALMS physical activity in a log (see Appendix D).

The overall purpose of the PALMS intervention was to (a) enhance self-efficacy for exercise, (b) increase physical activity through a supervised progressive strength and aerobic exercise program informed by studies conducted in older adults that gradually builds physical activity intensity and duration from baseline level up to 30 minutes of moderate intensity aerobic physical activity twice a week as recommended by the Canadian Physical Activity Guidelines for Persons with MS (CSEP, 2013) and (c) to determine the effects of the intervention on measures of cognitive function (clinical cognitive functioning, self-reported cognitive abilities and concerns, and neurocognitive functioning in everyday life), exercise self-efficacy, physical activity, depressive symptoms, and fatigue (Colcombe & Kramer, 2003; Latimer-Cheung, Martin Ginis, et al., 2013). Increased physical activity and exercise self-efficacy is fostered by development and practice of physical activity skills, exercise self-evaluation by keeping an exercise log, positive reinforcement, supportive coaching, and peer modeling by fellow group members or other gym members with visible functional limitations. Participants assigned to the attention-control group were offered six months access to

twice weekly, 60-minute long relaxation and stretching classes based on the National Multiple Sclerosis Society's Stretching for People with MS Manual (2012) led by a trained facilitator in a community setting. While stretching is movement, the intensity was kept low.

PROTECTION OF HUMAN SUBJECTS

The non-randomized controlled study was reviewed and approved by The University of Texas at Austin School of Nursing Departmental Review Committee and The University of Texas at Austin Institutional Review Board (IRB) for the protection of human subjects. The IRB approval letters and consent form are included in Appendix A and B. Potential subjects were told that their participation in the study was voluntary and that they could withdraw from the study at any time without recourse. They were informed about the study's purpose, its length (6-months), how many subjects were to be in the study and what they would be asked to do if they agree to participate. Possible benefits and risks associated with the study such as physical injury, temporary increases in their MS symptoms, becoming upset or frustrated during neurocognitive testing were discussed. Procedures and policies in place to protect the participant's privacy and confidentiality were explained. Participants were informed that they would not receive any type of payment for taking part in the study. Protections put into place against the risk of increasing depressive symptoms and suicidal ideation included providing each participant who met with the principal investigator a list of mental health agencies (names and phone numbers) in the Austin area developed by neuropsychology content expert and committee member, Dr. Andreana Haley. Additionally, the consent form

included language allowing the principal investigator to intervene should the participant exhibit an increase in depressive symptoms or suicidal ideation:

> "The risks associated with the study are that you might experience an increase in your feelings (depression, anxiety, and anger). We have provided you a list of counseling services available in the area if you need assistance. It is important that you understand that if you need assistance with the management of your emotions such as medication or counseling, you should talk to your healthcare provider about this. If you say during the study that you have thoughts of harming yourself, the principal investigator, Janet Morrison RN, MSN, will talk with you and contact your healthcare provider. Signing this consent document will give her permission to contact your healthcare provider if that situation should arise."

INSTRUMENTATION

Participants were pre-screened using a two-step process to determine their eligibility: 1) an initial phone interview using a script and the PAR-Q+ (Jamnik et al., 2011) to explore general health status and comorbid medical conditions and then for those meeting initial phone criteria 2) an in-person meeting to take the Symbol Digit Modalities Test to assess cognitive processing speed (Smith, 1982). Those meeting inclusion criteria were scheduled an in-person appointment to undergo baseline testing, which included the collection of self-report data, objective data, and neuropsychological testing data. The baseline self-report questionnaire packet (formatted using 16-point font) included: Background Information Sheet, Self-Administered Expanded Disability Status

Scale (Bowen et al., 2001; Kurtzke, 1983), Exercise Self-Efficacy Questionnaire (McAuley, 1993), Godin Leisure-Time Exercise Questionnaire (Godin & Shepard, 1985), Center for Epidemiologic Studies Depression Scale – Revised (Radloff, 1977), Modified Fatigue Impact Scale (Fisk, Pontefract, et al., 1994), PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales (Cella et al., 2007), and the 7-day Accelerometry Log (See Appendix D). Objective data were downloaded from an ActiGraph model wGT3X-BT accelerometer worn by the participant on the non-dominant waist/hip during waking hours for 7-days. After receipt of the 1) Verification of MS Diagnosis and 2) Physician Approval to Participate in the Physical Activity Program, a trained research assistant collected neurocognitive test data at an in-person meeting in The University of Texas at Austin Clinical Neuroscience Lab of the psychology department. The baseline neuropsychological test battery included: 2nd edition of the California Verbal Learning Test (standard form) [Delis et al., 2000], Revised Brief Visuospatial Memory Test (form 1) [Benedict, 1997], Controlled Oral Word Association Test (F-A-S form) [Benton et al., 1994], NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Oral Symbol Digit Test (Weintraub et al., 2013) and the Revised Everyday Problems Test (Willis et al., 1992).

Data were collected a second time (T2) three months after the start of the program (intervention or attention-control). The T2 questionnaire packet and accelerometer were given to the participant at their program meeting (intervention or attention-control). The T2 questionnaire packet contained: the Exercise Self-Efficacy Questionnaire (McAuley, 1993), Godin Leisure-Time Exercise Questionnaire (Godin & Shepard, 1985), Center for

Epidemiologic Studies Depression Scale – Revised (Radloff, 1977), Modified Fatigue Impact Scale (Fisk, Pontefract et al., 1994), PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales (Cella et al., 2007), and 7-day Accelerometry Log. The T2 neuropsychological test battery included: 2nd edition of the California Verbal Learning Test (alternate form) [Delis et al., 2000], Revised Brief Visuospatial Memory Test (form 2) [Benedict, 1997], Controlled Oral Word Association Test (C-F-L form) [Benton et al., 1994], NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Oral Symbol Digit Test (Weintraub et al., 2013) and the Revised Everyday Problems Test (Willis et al., 1992).

Data were collected a third and final time (T3) at the end of the 6-month program (intervention or attention-control). The T3 questionnaire packet and accelerometer was given to the participant at their last program meeting (intervention or attention-control). The T3 questionnaire packet contained: the Exercise Self-Efficacy Questionnaire (McAuley, 1993), Godin Leisure-Time Exercise Questionnaire (Godin & Shepard, 1985), Center for Epidemiologic Studies Depression Scale – Revised (Radloff, 1977), Modified Fatigue Impact Scale (Fisk, Pontefract, et al., 1994), PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales (Cella et al., 2007), and 7-day Accelerometry Log. The T3 neuropsychological test battery included: 2nd edition of the California Verbal Learning Test (standard form) [Delis et al., 2000], Revised Brief Visuospatial Memory Test (form 3) [Benedict, 1997], Controlled Oral Word Association Test (P-R-W form) [Benton et al., 1994], NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Oral

Symbol Digit Test (Weintraub et al., 2013) and the Revised Everyday Problems Test (Willis et al., 1992).

In addition to the data collected to evaluate the efficacy of the PALMS intervention described above, attendance and feasibility data were collected throughout the 6-month intervention using an attendance log and PALMS Intervention Log (see Appendix D).

Physical Activity Readiness Questionnaire for Everyone

The PAR-Q+ is an evidence-based questionnaire designed to facilitate the clearance process for physical activity participation among asymptomatic populations as well as persons with chronic diseases or conditions. The PAR-Q+ was recently developed by an expert panel to address concerns from healthcare providers and fitness professionals regarding the utility and effectiveness of the Physical Activity Readiness Questionnaire (PAR-Q) (Jamnik et al., 2011; Warburton et al., 2011). The PAR-Q+ contains seven general health questions followed by a section of questions probing for the presence and impact of chronic medical conditions (e.g., back problems, cancer, cardiovascular, pulmonary and metabolic disease). Data collected from the PAR-Q+ is reported in the study flow diagram under the number excluded prior to group assignment.

Symbol Digit Modalities Test (Oral administration)

The SDMT uses a key of nine abstract geometric symbols paired with a single digit number to assess cognitive processing speed (Smith, 1982). The participant is given 90 seconds to verbalize the digit paired to each of 110 quasi-randomized symbols printed

on a single sheet of 8.5 x 11-inch paper with the key printed at the top. The total score derived is the number of correct responses recorded by the tester in 90 seconds. A score of 55 or less has been suggested as an effective screen to classify patients with MS as cognitively impaired versus unimpaired with high reliability, good sensitivity (0.82) and specificity (0.60) (Benedict et al., 2012; Parmenter, et al., 2007). High test-retest reliability (r = 0.97) has been reported for persons with MS (Benedict, 2005). The SDMT has been validated as part of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS) battery with very large effect size reported ($d = 1.31$, $p < .001$) discriminating MS patients and healthy controls (Benedict, Cookfair, et al., 2006).

Accelerometry

Accelerometers are a type of motion sensor worn on the wrist, ankle or waist to measure physical activity and energy expenditure (Motl et al., 2006). Activity counts derived from accelerometers have been identified as the benchmark measure of ambulation in persons with neurologic diseases (Pearson et al., 2004). Extensive evidence of the validity and reliability has been provided for persons with MS using model 7164 and model GT3X manufactured by the ActiGraph™ company (ActiGraph™, Pensacola, FL) (Gosney, Scott, Snook, & Motl, 2007; Motl et al., 2006; Motl et al., 2010). Activity output cut-points for quantifying time spent in sedentary, light and moderate-to-vigorous physical activity have been established in persons with MS using both the 7164 and GT3X models of accelerometers from ActiGraph™ (Sandroff, Motl, & Suh, 2012). ActiGraph™ model wGT3X-BT was used in this study (model 7164 and GT3X models have been discontinued). The device captures and records high-resolution human activity

information using a solid-state 3-axis accelerometer and proprietary filtering algorithm (ActiGraph™, 2016). Data from the devices were downloaded onto a PC via an ActiLife USB cable into the ActiLife 6 software. The software converts the raw data file into a proprietary *.agd file. The *.agd file data was validated for weartime then scored using the cut-points defined by Sandroff et al. (2012). Raw, *.agd, weartime, and scored counts/cuts files were created and saved onto password protected devices (PC and jump drive). Mean sedentary, light, and moderate-to-vigorous activity counts as well as step counts from days with 600+ minutes of wear time at baseline, T2 and T3 were entered into SPSS.

Background Information Sheet

The background information sheet was used to collect demographic characteristics to describe the sample and to evaluate the equivalence between the intervention and attention-control groups. Data collected included: age, gender, race, ethnicity, years of education, employment status, MS duration and course (relapsing-remitting, secondary-progressive, primary-progressive, or progressive-remitting).

Self-Administered Expanded Disability Status Scale

Bowen, Gibbons, Gianas, and Kraft (2001) developed the self-administered modification of Kurtzke's Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The self-administered form was found to have strong intraclass correlation coefficient to the EDSS using gait alone ($r = 0.89$) or EDSS using functional systems ($r = 0.87$) compared to physician-administered form (Bowen et al., 2001). While Kurtzke's EDSS has been

the subject of both reliability and validity concerns, it is undeniably the most widely used method to quantify MS-related functional disability by clinicians and researchers alike (Bowen et al., 2001; Schwartz, Vollmer, & Lee, 1999). Scores derived from the EDSS range from 0 (normal neurologic function) to 10 (death due to MS) with a score of 4.5 reflecting the ability to "walk without aid or rest for some 300 meters" (Kurtzke, 1983, p. 1446).

Exercise Self-Efficacy Scale

This is a six-item self-report questionnaire used to measure participants' level of confidence in being able to exercise (0% - not confident at all to 100% - highly confident) for 20 plus minutes three times a week at moderate intensity for the next one to six months (McAuley, 1993). Score validity and reliability have been supported in studies of persons with MS (Motl & McAuley, 2009).

Godin Leisure-Time Exercise Questionnaire

This is a self-report measure of physical activity that is used in clinical and epidemiologic studies (Godin & Shepard, 1985). The GLTEQ is a two-item measure of usual physical activity. The first item measures frequency of physical activity by asking the number of times per week the person does strenuous (heart beating rapidly, e.g. running), moderate (not exhausting, e.g. fast walking), and mild (minimal effort, e.g. easy walking) physical activity for more than 15 minutes during their free time in a typical week. These frequencies are multiplied by nine, five, and three metabolic equivalents (METS), respectively, and summed to determine a measure of total leisure activity: active

- 24 METS or more, moderately active - 14 to 23 METS, or insufficiently active - less than 14 METS (Godin, 2011). The second item asks how frequently (often, sometimes, never/rarely) the person engages in physical activity long enough to produce sweat during a typical week. Validity of the GLTEQ has been established in samples of healthy adults and in samples of persons with MS (Amireault & Godin, 2015; Gosney et al., 2007; Jacobs, Ainsworth, Hartman, & Leon, 1993; Miller, Freedson, & Kline, 1994; Motl et al., 2006).

Center for Epidemiologic Studies Depression Scale

The CES-D is a measure of depressive symptoms (Radloff, 1977). Evidence supports the validity of the CES-D as a measure of depressive symptoms with demonstrated internal consistency (α =. 90) in a sample of 696 persons with MS (Verdier-Taillefer et al., 2001). Individual items on this 20-item summated rating scale are rated from 0 to 3 with the total score ranging from 0 to 60. Higher scores indicate more depressive symptoms during the past week. The scale is commonly used to classify people scoring 15 or less as having no depression and those scoring 16 or above indicating elevated depressive symptomology (Radloff, 1977; Verdier-Taillefer et al., 2001).

Modified Fatigue Impact Scale

The MFIS is a 21-item measure of physical, cognitive, and psychosocial function effects of fatigue in persons with MS adapted from the Fatigue Impact Scale (Fisk, Pontefract et al., 1994). Total and subscale scores are computed with responses scored: 0

= never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = almost always. Higher scores indicate greater perceived fatigue. The total scale consists of 21 items with scores ranging from 0 to 84. The physical subscale has nine items with scores ranging from 0 to 36, the cognitive subscale has ten items with scores ranging from 0 to 40, and the psychosocial subscale has two items with scores ranging from 0 to 8. Face validity and internal consistency ($\alpha = .80$) for the modified form has been reported previously (Fisk, Ritvo et al., 1994). More recently, Cronbach's alpha reliabilities for the total scale ($r = .81$), physical ($r = .91$), cognitive ($r = .95$), and psychosocial ($r = .81$) subscales have been reported (National Multiple Sclerosis Society, 1997).

Patient-Reported Outcome Measurement Information System (PROMIS) – Cognitive Abilities and Concerns Scales

Two instruments were used to assess self-reported cognitive function: PROMIS v1.0-Applied Cognition-Abilities-Short Form 8a and PROMIS v1.0-Applied Cognition-General Concerns-Short Form 8a. These instruments were developed using Item Response Theory, which links item responses to latent traits (e.g., cognitive abilities, cognitive concerns) (Cella et al., 2007). Reeve et al. (2007) and Cella et al. (2010) provide evidence supporting the psychometric properties of the PROMIS item banks in the general population as well as clinical groups. Becker, Stuifbergen and Morrison (2012) provide additional evidence of acceptable psychometric properties for the PROMIS cognitive abilities and concerns scales in a sample of community-dwelling persons with MS.

The 8-item positively worded cognitive abilities scale assesses perceived

cognitive abilities (e.g., attention, thinking, memory) over the preceding 7 days. Item responses range from 1 (Not at all) to 5 (Very much). The total score is the sum of item responses, which range from 8 to 40. Higher scores represent greater perceived cognitive ability.

The 8-item negatively worded cognitive concerns scale assesses perceived cognitive concerns (e.g., slow thinking, trouble concentrating) over the preceding 7 days. Item responses range from 1 (Never) to 5 (Very often – Several times a day). The total score is the sum of item responses, which also range from 8 to 40. Higher scores represent greater perceived cognitive concerns.

California Verbal Learning Test

The CVLT-II is a test of auditory/verbal memory (Delis et al., 2000). A list of 16 words is read aloud to the subject who has been instructed to listen to the list then repeat aloud as many as possible. Five trials are conducted with the examiner presenting the 16-word list aloud each time and recording the number of correct responses after each trial. A second list of 16 words is presented and after a 25-minute delay the subject recalls as many words as possible then responds to a yes/no recognition test of the second list. Total and delayed-recall scores are reported. Two forms of the test, standard and alternate, are available for serial testing. Acceptable test-retest reliability (r = 0.78) has been reported for the CVLT-II in persons with MS (Benedict, 2005). The CVLT-II has been validated as part of the MACFIMS battery with large effect sizes reported for the Total Recall (d = .70, $p < .001$) and Delayed Recall scores (d = .79, $p < .001$) discriminating MS patients and healthy controls (Benedict, Cookfair, et al., 2006).

Brief Visuospatial Memory Test

The BVMT-R is a test of visual/spatial learning and memory (Benedict, 1997). The subject is instructed to view a piece of paper showing six graphic figures arranged in a 2 x 3 matrix for 10 seconds before the stimulus is withdrawn from view. The subject then takes as much time as needed to draw from memory the six figures on a blank 8.5 x 11-inch piece of paper using a pencil. Three trials are conducted followed by a 25-minute delayed recall and yes/no recognition trial. The six-figure trials are judged on accuracy and location. Each figure is given 0 to 2 points with the total score ranging from 0 to 12. The Total Recall score is the sum of raw scores from the first three trials. The Delayed Recall is the raw score of the 25-minute delayed recall trial. Six alternate forms exist for serial testing. Good test-retest reliability (r = 0.91) has been reported for the BVMT-R in persons with MS (Benedict, 2005). The BVMT-R has been validated as part of the MACFIMS battery with very large effect sizes reported for the Total Recall (d = 1.04, p < .001) and Delayed Recall scores (d = 1.07, p < .001) discriminating MS patients and healthy controls (Benedict, Cookfair, et al., 2006).

Controlled Oral Word Association Test

The COWAT is a test of verbal fluency and word finding (Benton et al., 1994). Subjects are given three separate trials of 60 seconds to articulate as many words as they can that start with one of three stimulus alphabet letters (F-A-S). Alternate forms using three different letters (C-F-L and P-R-W) are available for serial testing. The total score is the number of different words generated across the three trials. Test-retest reliability examined at one-week intervals in 34 persons with MS was high (r = .90) (Benedict, Cox,

et al., 2004). The COWAT has been validated as part of the MACFIMS battery with a medium effect size reported ($d = 0.53$, $p < .001$) discriminating MS patients and healthy controls (Benedict, Cookfair, et al., 2006).

Flanker Inhibitory Control & Attention Test

The Flanker is a test of attention as well as inhibition of automatic response tendencies that tend to interfere with goal achievement. This test is part of the NIH Toolbox, a computer-administered battery of brief neuropsychological tests designed for use as outcome measures in epidemiologic, longitudinal and clinical trial studies (Gershon et al., 2013). Test-retest reliability, convergent and discriminant validity derived from an English speaking representative sample of 476 participants has been reported for all of the NIH Toolbox instruments (Weintraub et al., 2013). The Flanker consists of 20 trials where the participant is asked to indicate the direction of the middle stimulus (< or >) using the keyboard arrow key corresponding the stimulus. The task requires the participant to inhibit attention to stimuli adjacent to the middle stimulus. The middle stimulus is randomly presented congruently or incongruently to the "flanking" stimuli. The Flanker test takes about 3 minutes to administer and produces several scores: computed accuracy + reaction time score, age-adjusted scale score, fully-adjusted scale score, and national percentile ranking. The computed accuracy + reaction time score was used in the analysis since the goal of this study is to ascertain individual and group differences rather than comparisons to normative data.

Oral Symbol Digit Test

The OSD, also part of the NIH Toolbox, is a computerized version of the Oral Symbol Digit Test that assesses processing speed (mental efficiency) – the amount of time it takes to process a set amount of information (Weintraub et al., 2013). Participants are shown a key of nine abstract symbols paired with a number from 1 to 9. They use the key to verbally indicate which number goes with each symbol presented in a long string of 144 symbols on the computer screen. The participant is given 120 seconds to call out the number matching each symbol, in order, without skipping, as fast as possible. The score is the number of correct responses given ranging from 0 to 144.

Everyday Problems Test

The Everyday Problems Test-Revised (EPT-R) is a measure of neurocognitive functioning in everyday life developed in a study of elders (Willis et al., 1992). The revised 30-item EPT-R assesses performance in seven areas: household management, transportation, financial management, shopping, phone use, medication use, and nutrition and meal preparation. Internal consistency and 2-month test/retest reliability for the EPT-R were greater than 0.83 after pilot testing in a sample of 29 persons with MS (Becker et al., 2012). Construct and convergent validity were established in the original study with elders (Willis et al., 1992). The EPT-R holds promise for being sensitive to change after interventions designed to promote cognitive function in persons with MS (Becker et al., 2012).

PALMS Intervention Log

The PALMS Intervention Log was used to collect physiologic and subjective data to evaluate the feasibility of the intervention program (See Appendix D). Data collected included: heart rate and ratings of perceived exertion using the 10 point modified Borg scale taken every 10 minutes starting at baseline then throughout the intervention session. At the end of the intervention session participants were asked how they felt on a 10-point scale (+5 = very good, 0 = neutral, to – 5 = very bad), rated their physical and mental fatigue on a 0 (none) to 10 (strongest feeling) scale, and rated how much they enjoyed the session from 1 (not at all) to 7 (very much). Brief qualitative notes were taken to document participant behavior and/or comments.

PALMS Physical Activity Log

The PALMS Physical Activity Log was given to intervention participants to collect self-report data on the frequency, type and length (in minutes) of physical activity the intervention group participants do outside of the PALMS intervention sessions. Participants took the form home with them but did not fill it out and return it to the principal investigator despite several gentle requests.

Table 3. Summary of Study Instruments

Instrument	Variable(s)	Subscales	Number
Physical Activity Readiness Questionnaire Plus [PAR-Q+] (Jamnik et al., 2011)	Health-related physical activity risk	N/A	16-items
Symbol Digit Modalities Test[1] [SDMT] (Smith, 1982)	Psychomotor speed, attention/integration	N/A	110-trials
Accelerometry - ActiGraph™ model wGT3X-BT	Physical activity: sedentary, light, moderate-to-vigorous activity, and step counts	N/A	N/A
Background Information Sheet	Demographic data and MS characteristics	N/A	14-items
Self-Administered Expanded Disability Status Scale[1] [EDSS] (Bowen et al., 2001; Kurtzke, 1983)	Functional disability based on eight functional systems: ambulation, pyramidal, cerebellar, sensation, bladder/bowel, vision, brainstem, and cerebral	N/A	42-items
Exercise Self-Efficacy Questionnaire [ExSE] (McAuley, 1993)	Exercise self-efficacy	N/A	6 items
Godin Leisure-Time Exercise Questionnaire [GLTEQ] (Godin & Shepard, 1985)	Physical activity	N/A	4 items
Center for Epidemiologic Studies Depression Scale-Revised [CES-D] (Radloff, 1977)	Depressive symptoms	N/A	20 items
Modified Fatigue Impact Scale [MFIS] (Fisk, Pontefract et al., 1994)	Perceived fatigue	Total Scale	21 items
		Physical subscale	9 items
		Cognitive subscale	10 items
		Psychosocial subscale	2 items
PROMIS Cognitive Abilities (Cella et al., 2007)	Self-reported cognitive abilities	N/A	8 items
PROMIS Cognitive Concerns (Cella et al., 2007)	Self-reported cognitive concerns	N/A	8 items
California Verbal Learning Test[1] [CVLT-II] (Delis et al., 2000)	Auditory/verbal learning	Total Recall	5 trials
		Delayed recall	1 trial
Brief Visuospatial Memory Test[1] [BVMT-R] (Benedict, 1997)	Nonverbal learning and memory	Total Recall	3 trials
		Delayed recall	1 trial

Table 3. Summary of Study Instruments (continued)

Instrument	Variable(s)	Subscales	Number
Controlled Oral Word Association Test [COWAT] (Benton et al., 1994)	Verbal fluency and word finding	N/A	1 trial
NIH Toolbox - Flanker Inhibitory Control & Attention Test[2] [Flanker] (Weintraub et al., 2013)	Executive function, visuospatial attention, and inhibitory control	N/A	1 trial – 20 stimuli
NIH Toolbox - Oral Symbol Digit Test[2] [OSD] (Weintraub et al., 2013)	Processing speed	N/A	1 trial – 144 stimuli
Everyday Problems Test-Revised[1] [EPT-R] (Willis et al., 1992)	Self-reported neurocognitive functioning in everyday life	N/A	30 items
PALMS Intervention Log	Log maintained by investigator to evaluate participant response to PALMS intervention sessions	N/A	22 items
PALMS Physical Activity Log	Participant log to evaluate frequency, duration, and mode of physical activity outside of PALMS intervention sessions	N/A	Daily

1=Proprietary; 2=Proprietary/Online only

DATA ANALYSIS

All analyses were conducted using SPSS Statistics version 23 (IBM, 2015). Data were checked for accuracy and evaluated for violations of statistical tests described below. If assumptions were violated, alternative tests were used if available. Internal consistency reliability was determined for each instrument (as appropriate) yielding reliability coefficients of .79 and above. Descriptive data analyses were performed to obtain a profile of the sample on demographic and illness-related variables. The groups were compared at baseline on demographic and disease variables; if differences were found, these variables were considered as covariates in the analyses described below. The significance level for all tests was .05. Analyses were conducted using the "intention to treat" principle (Hollis & Campbell, 1999). Physical activity data were downloaded from

the accelerometers worn for seven days at baseline, 3-months, and 6-months (post-intervention).

RQ 1.

What is the feasibility of delivering a small group moderate-intensity exercise program for persons with MS over a 6-month time period?

RQ 1.1.

What is pattern of response to and enrollment in the study?

RQ 1.2.

What is the attendance pattern across the 6-months for the intervention and attention-control groups?

RQ 1.3.

What is the frequency, duration, and mode of physical activity documented in the PALMS physical activity log?

RQ 1.4.

How do participants respond to the PALMS intervention (heart rate, ratings of perceived exertion, physical and mental fatigue, general wellbeing, and enjoyment)?

The feasibility of conducting the intervention was assessed using process evaluation methods and descriptive statistics (e.g., frequencies, percentages). Data were collected using recruitment and attendance logs to examine the processes of (a) recruiting, (b) enrolling participants and (c) delivering the intervention. The recruitment log documented where letters were sent, notices posted, and recruiting presentations made. Inquiries received were queried as to which recruitment method they were responding to, whether the inquirer was subsequently enrolled, and into which arm of the study they were assigned.

RQ 2.

What are the effects of the Physically Active Lifestyle in MS (PALMS) intervention?

RQ 2.1.

What are the within-group, between-groups, and group-by-time interaction effects on the primary outcomes of clinical cognitive function (California Verbal Learning Test [CVLT], Brief Visuospatial Memory Test [BVMT], Controlled Oral Word Association Test [COWAT], NIH Toolbox Flanker Inhibitory Control and Attention Test [Flanker], NIH Toolbox Oral Symbol Digit Test [OSD]), self-reported cognitive abilities and concerns (Patient-Reported Outcomes Measurement Information System [PROMIS] v1.0 Cognitive Abilities and Cognitive Concerns Scales), and neurocognitive function in everyday life (revised Everyday Problems Test [EPT-R]) (Benedict, 1997; Benton et al., 1994; Cella et al., 2007; Delis et al., 2000; Weintraub et al., 2013; Willis et al., 1992)?

RQ 2.2.

What are the within-group, between-groups and group-by-time interaction effects on the secondary outcomes of exercise self-efficacy [ExSE], physical activity [GLTQ and accelerometer counts: sedentary, light, moderate-to-vigorous physical activity, and steps], depressive symptoms [CES-D], and fatigue [MFIS] (Fisk, Pontefract et al., 1994; Godin & Shepard, 1985; McAuley, 1993; Pearson et al., 2004; Radloff, 1977)?

To determine the effect of the PALMS intervention on the outcome measures - California Verbal Learning Test (CVLT), Brief Visuospatial Memory Test (BVMT), Controlled Oral Word Association Test (COWAT), NIH Toolbox Flanker Inhibitory

Control and Attention Test (Flanker), NIH Toolbox Oral Symbol Digit Test (OSD), PROMIS Cognitive Abilities and Cognitive Concerns Scales, revised Everyday Problems Test (EPT-R), Exercise Self-Efficacy Questionnaire (ExSE), Godin Leisure-Time Exercise Questionnaire (GLTEQ), Accelerometer counts (sedentary, light, moderate-to-vigorous physical activity, steps), Center for Epidemiologic Studies Depression Scale-Revised (CES-D), and Modified Fatigue Impact Scale (MFIS) - a 2 (intervention and control) by 3 (baseline, 3-month and 6-month post-intervention data) mixed effects analysis of variance design was used (Benedict, 1997; Benton et al., 1994; Cella et al., 2007; Delis et al., 2000; Fisk, Pontefract et al., 1994; Godin & Shepard, 1985; McAuley, 1993; Radloff, 1977; Weintraub et al., 2013; Willis et al., 1992). The multivariate approach to repeated measures was applied to avoid the more stringent assumptions of the univariate model. Each outcome was analyzed separately. Because this was a pilot feasibility study with a small sample size (N = 16), there is increased risk of making a type II error. Therefore, the α level for all analyses remained at the .05 level rather than adjusting for experiment wide error (Lipsey, 1990). The test of the time-by-group interaction was assessed for differences in gains over time between the experimental and control groups on the primary and secondary outcomes. Effect sizes for all analyses were calculated (η^2) to provide data for future studies with larger sample sizes.

SUMMARY

This chapter provided a description of the methods that were used to collect and analyze the data in this quasi-experimental study, which focused on the feasibility and effects of a six-month program of supervised physical activity. The study investigated

clinical cognitive function, self-reported cognitive abilities and concerns, and cognitive function in everyday life as primary outcomes as well as exercise self-efficacy, physical activity, depressive symptoms and fatigue as secondary outcomes. Data was collected at baseline, 3-months and at 6-months (immediately post-intervention). Descriptive statistics, mixed effects analysis of variance and determination of effect size using SPSS 23.0 (IBM, 2015) was employed to address the research questions posed in this study.

Chapter 4: Results

Chapter 4 presents the results of this dissertation study. The first section presents the results derived from screening the data and assessing scale reliability. The second section profiles the study sample (n=16) on demographic and illness-related variables using descriptive statistics. This section also presents data comparing the intervention (n=8) and attention-control (n=8) groups at baseline. The third section presents analyses of the first research question related to the feasibility of the PALMS study. The final section presents the results of analyses examining the effects of the PALMS study.

DATA SCREENING

Data were extracted from questionnaires, neuropsychological test records, and ActiGraph accelerometers collected at baseline, T2 (3 months), and T3 (6 months) immediately after the intervention ended. Attendance data were collected over the course of the study for all participants (n=16) while data for the participants in the intervention group (n=8) were extracted from each participant's PALMS intervention log. Data were entered into and analyzed using IBM SPSS Statistics version 23 for Windows. Analyses were conducted using the "intention to treat" principle (Hollis & Campbell, 1999). Baseline values were copied and pasted into T2 and T3 for the single individual who dropped out of the study. The SPSS data file was proofread against the original data for accuracy by the principal investigator and a volunteer. Univariate descriptive statistics were examined for missing data, out-of-range values, plausible means and standard deviations as outlined by Tabachnick and Fidell (2013).

Cronbach's alpha coefficient, a measure of internal consistency reliability, was determined to be greater than .83 at baseline, 3- and 6-months for the three summed

scales with fewer items than participants used in this study: ExSE, PROMIS cognitive abilities and concerns (Cella et al., 2007; Godin & Shepard, 1985). Alpha coefficients greater than 0.70 support the proposition that the items in a scale 'hang together' and reflect the same underlying construct (Warner, 2013). Internal consistency reliability was not appraised for the 21-item MFIS or 20-item CES-D since alpha coefficients tend to be imprecise (inflated) and not accurately reflect the population when the sample size is smaller than the number of items in a scale (Charter, 2003; Fisk, Pontefract et al., 1994; Radloff, 1977).

Table 4.1 Internal Consistency Reliability

Instrument	# of Items	Cronbach's Alpha Coefficient		
		Baseline (n=16)	T2 (3-months) (n=16)	T3 (6-months) (n=16)
ExSE	6	0.97	0.99	0.99
PROMIS Cognitive Abilities	8	0.93	0.92	0.92
PROMIS Cognitive Concerns	8	0.96	0.88	0.83

ExSE = Exercise Self-Efficacy Scale

SAMPLE

Demographic characteristics of the participants successfully recruited into this study are as follows: the sample was primarily female (n = 11) and middle-aged with mean age of 45.6 $\pm$ 9.1 years. The sample was mostly White (n=11) but included three African American and three Hispanic participants. Marital status varied among the sample: eight were married, four had never been married, two were divorced, one separated, and one lived with a significant other. Educational achievement among the sample was high; 12 had college degrees (associates to graduate) and four had graduated from high school. Employment was diverse: four worked full-time, four part-time, four

were unemployed due to disability, two were full-time homemakers, one was a full-time homemaker who also had a part-time job, one was unable to find work because of where she lived. Over 80% of the sample described their MS course as relapsing-remitting while two indicated primary progressive and another secondary progressive MS. Neurologic functional status was characterized using the self-reported form of Kurtzke's Expanded Disability Statues Scale [EDSS] (Bowen et al., 2001, Kurtzke, 1983). Scores ranged from 3.0 to 6.0 on the 0 - 10 EDSS scale ('normal neurologic function' to 'death ascribed to MS', respectively). Mean EDSS score for the sample was 4.5 ± 1.1. Scores less than 4.0 reflect mild MS, scores 4.0 to 5.5 moderate MS, and scores 6.0 and higher indicate severe MS (Oynhausen et al., 2014). Ambulatory aides, such as the use of a single cane, are heavily weighted in the EDSS system garnering a score of 6.0 or higher even though other neurologic functional systems (cognition, vision, sensation, balance, strength, bladder/bowel, brainstem) may be relatively intact. The four participants with total EDSS scores of 6.0 used a single cane when ambulating. Cognitive function impairment was appraised using the Symbol Digit Modality Test (SDMT) administered prior to enrollment. Participants had an average score of 41.7 ± 10.0 with scores ranging from 20 to 56.

Table 4.2 Sample Demographics (N=16)

Characteristic		n	%	Mean (SD)	Range
Age (years)		16		45.6 (9.1)	31-58
MS duration (years)		16		11.5 (8.3)	<1-29
Education (years)		16		16.6 (2.6)	12-20
EDSS score		16		4.5 (1.1)	3.0-6.0
SDMT score		16		41.7 (10.0)	20-56
Gender	Female	11	69		
	Male	5	31		
Race	White	13	81		
	African American	3	19		
Ethnicity	Hispanic	3	19		
	Non-Hispanic	13	81		
Marital Status	Married	8	50		
	Never married	4	25		
	Divorced	2	13		
	Separated	1	6		
	Living with significant other	1	6		
Highest Education	High school diploma	4	25		
	Associates degree	3	19		
	Bachelors degree	6	38		
	Graduate degree (masters or doctorate)	3	19		
Employment	Work full-time	4	25		
	Work part-time	4	25		
	Homemaker full-time	2	13		
	Homemaker full-time + part-time job	1	6		
	Unemployed due to disability	4	25		
	Unable to find suitable work	1	6		
MS Course	Relapsing-Remitting	13	81		
	Primary Progressive	2	13		
	Secondary Progressive	1	6		

Baseline data for demographic and illness variables were examined for group equivalence. Continuous level variables examined include: age, years of education, MS duration, EDSS scores and SDMT scores. Nominal level variables examined include: gender, race, ethnicity, marital status, highest education, employment, and MS course.

A number of outliers were identified and the Shapiro-Wilkes test of normality was not met for all continuous variables. Therefore, both parametric (independent-samples *t*-test) and nonparametric (Mann-Whitney *U* test) procedures were used. Results from parametric ($t > .05$) and nonparametric tests ($U > .05$) support accepting the null hypothesis:

H_o: the means for the selected variables (age, MS duration, EDSS, SDMT, years of education) for the intervention and attention-control groups are equal (i.e., $\mu_1 = \mu_2$)

Nominal level variables were examined using descriptive statistics. Assumptions for using a chi-square or related test (Fisher's exact or McNemar's test) were not met due to the small sample size, which require cell size frequencies greater than 10 (Plitchta, Kelvin, & Munro, 2013, p. 290). The intervention and attention control groups were reasonably alike for gender, marital status, highest education attained, employment, and MS disease course. The two groups were less similar for race or ethnicity. The attention control group was 100% White while the intervention group, with three African Americans, was 63% White. The three Hispanic participants were in the attention-control group while the intervention group was 100% non-Hispanic. The data presented below were collapsed into larger categories for clarity.

Table 4.3 Group Demographics

		Intervention (n=8)			Attention-Control (n=8)		
Characteristic		n	%	Mean (SD)	n	%	Mean (SD)
Gender							
	Female	5	63%		6	75%	
	Male	3	38%		2	25%	
Race							
	White	5	63%		8	100%	
	African American	3	38%		0	0%	
Ethnicity							
	Hispanic	0	0%		3	38%	
	Non-Hispanic	8	100%		5	63%	
Marital Status							
	Married or living with a significant other	4	50%		4	50%	
	Never married, divorced or separated	4	50%		4	50%	
Employment							
	Work full- or part-time	4	50%		5	63%	
	Do not work outside of the home	4	50%		3	38%	
MS Course							
	Relapsing-Remitting	6	75%		7	88%	
	Progressive	2	25%		1	13%	
Education							
	High school diploma	1	13%		3	38%	
	Associates, bachelors, or graduate degree	7	88%		5	63%	
	Total years	8		16.6 (2.2)	8		15.5 (3.1)
EDSS							
	Total score	8		4.0 (1.1)	8		4.7 (1.4)
SDMT							
	Total score	8		43.0 (7.9)	8		40.4 (12.3)

FEASIBILITY OF THE PALMS STUDY

RQ 1.

What is the feasibility of delivering a small group moderate-intensity exercise program for persons with MS over a 6-month time period?

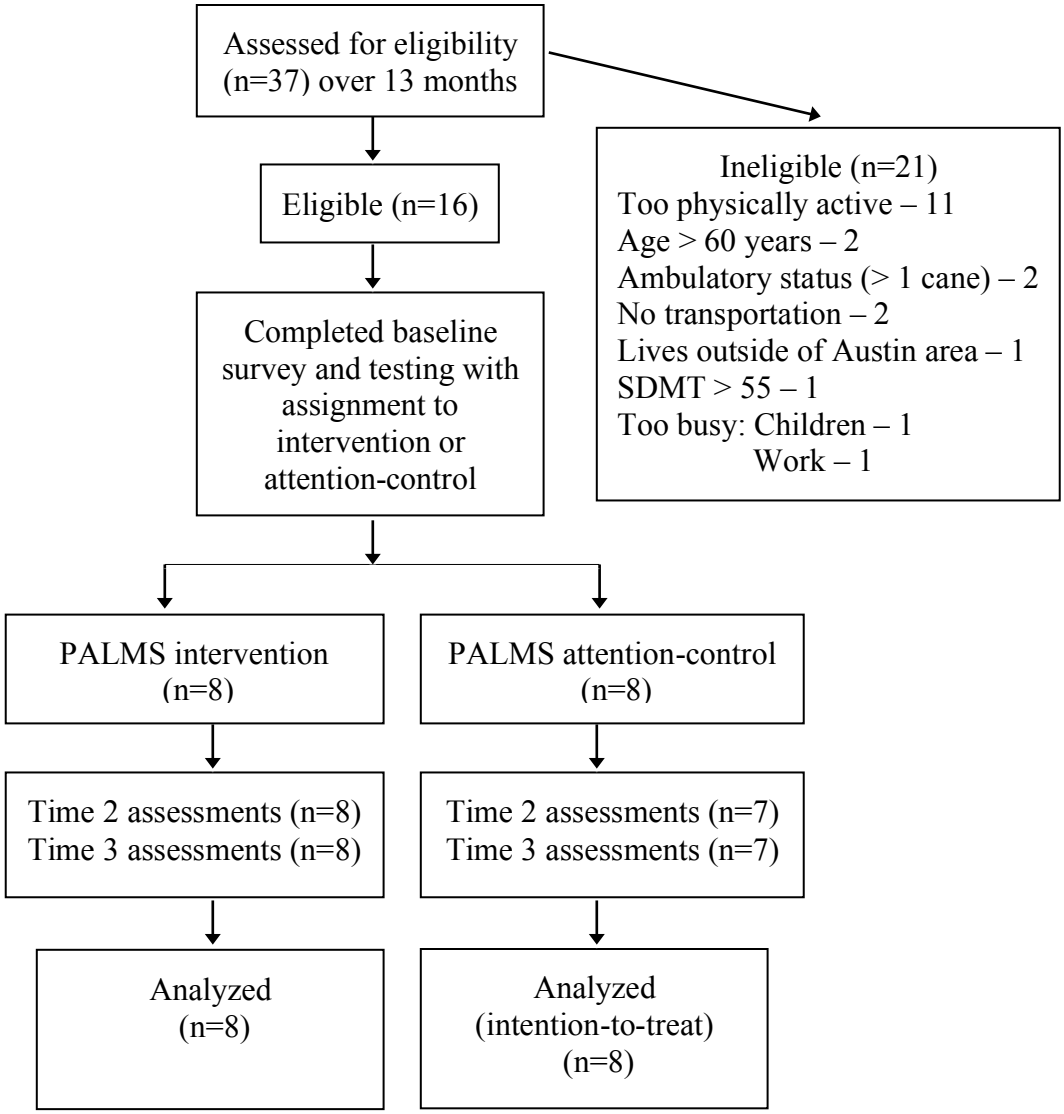
RQ1.1.

What is the pattern of response to and enrollment in the study?

Study participants were recruited through several strategies implemented over 13 months (November, 2014 to December, 2015). The largest number of participants heard about the study from 10 presentations the PI made to National MS Society (NMSS) support groups (n=7). The other 9 participants heard about the study through emails sent to NMSS support members by the group leaders (n=3), referrals from MS neurologists and nurses (n=3), personal referrals from study participants (n=2), as well as YMCA staff (n=1). The first six participants were recruited from November 2014 to February 2015. While most (n=12) of those expressing interest in the study by calling or emailing the PI were enrolled within one month's time, four participants were enrolled many months (8 to 11 months) after initially expressing interest.

Thirty-seven individuals contacted the PI to express interest in participating in the study. Reasons for not being deemed eligible to participate in the study included: being too physically active (n=11), age over 60 (n=2), using more than one cane to ambulate (n=2), not having transportation to get to the intervention or attention-control site (n=2), living outside of the Austin area (n=1), scoring well above the 55 cut point on the SDMT (n=1), or being too busy to attend twice weekly classes for 6 months (n=2).

Figure 4.1 PALMS Flowchart



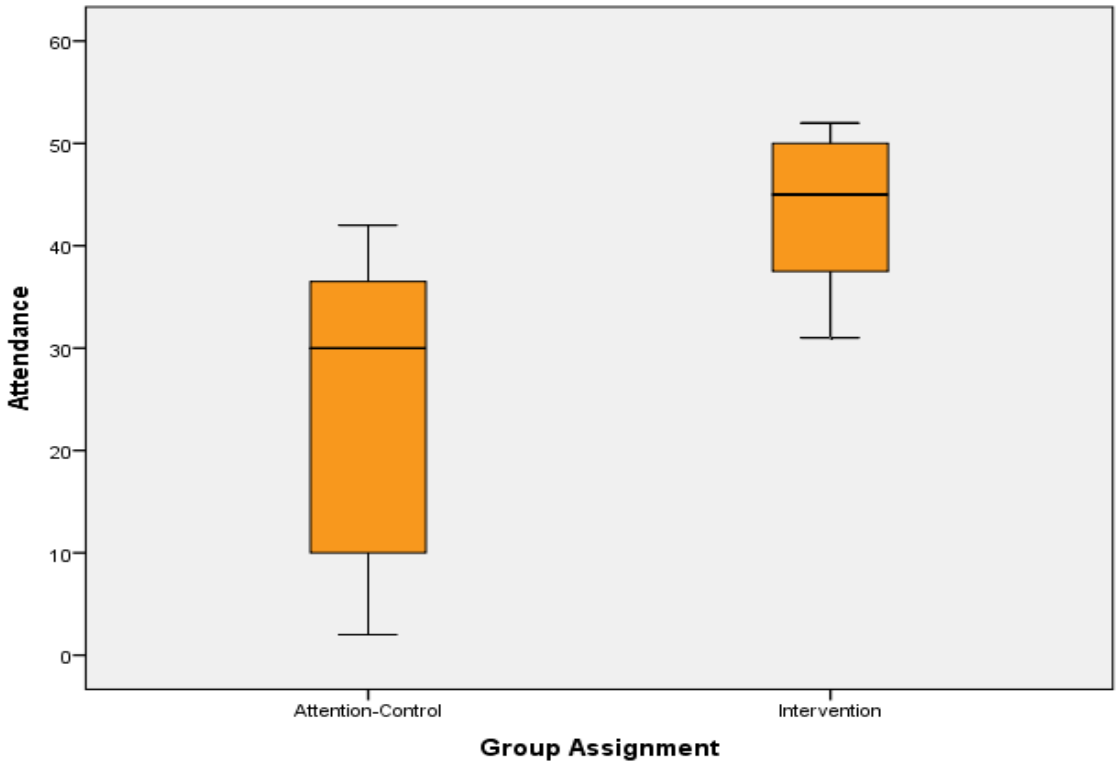
RQ 1.2.

What is the attendance pattern across the 6-months for the intervention and attention-control groups?

Participants were offered a total of 52 classes (two classes a week for 6 months). The 8 participants assigned to the intervention group attended an average of 43.5 $\pm$ 7.93 classes; range 31 to 52 classes (60% - 100%). The 8 participants assigned to the attention-control group attended an average of 24.6 + 15.19 classes; range 2 to 42 classes (4% to 81%). Attendance for the two groups was significantly different, $t(14) = -3.12$, $p<.01$.

Absence patterns varied between the two groups. Seven of the 8 intervention group participants had no discernable pattern among class absences while one was unable to attend classes 39-52 after moving to San Antonio. This participant attended three classes after her move even though the drive to the YMCA was more than an hour each way in rush hour traffic and she had worked all day. In the attention-control group, one participant attended the first two classes before dropping out of the study. Another participant in this group notified the PI that he was unable to continue attending classes due to work obligations (part-time occasional job). He had attended 8 classes over 13 weeks. The remainder of the group's absences had no discernable pattern.

Figure 4.2 Group Attendance



RQ1.3.

What is the frequency, duration, and mode of physical activity documented in the PALMS physical activity log?

Participants in the intervention group were asked to keep a log of physical activities done outside of the twice-a-week meetings with the PI. The PI provided participants copies of the log (see Appendix D). Despite numerous prompts and reminders from the PI, none of the eight participants completed the log. Therefore, the PI

routinely asked participants what they had done outside of class and made notes in their PALMS Intervention Log. While some of the participants occasionally remarked that they had taken short walks with their family, gone to a park, or ridden a bike; few participated in additional physical activities outside of class.

RQ 1.4.

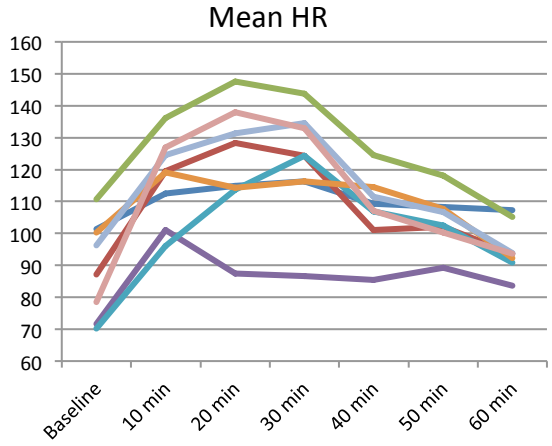
How do participants respond to the PALMS intervention (heart rate, ratings of perceived exertion, physical and mental fatigue, general wellbeing, and enjoyment)?

Data were collected at each intervention class to monitor and assess level of exercise intensity. Baseline resting heart rate was used to calculate goal heart rate range (40-60% of heart rate reserve) for each participant. Participants wore a Polar® FT-1 heart monitor around their chest which displays continuously on the FT-1 wrist unit. Participants were asked, "How hard do you feel you are working?" using the 10-point Berg Scale Heart rate to determine their rating of perceived exertion [RPE] (Borg, 1998). Heart rate and RPE were assessed at the beginning of each class and every 10 minutes thereafter and documented in the participant's PALMS activity log.

The majority of participants (n=5) attained a heart rate within their goal heart rate range at every class. One participant achieved their goal at 96% of the classes, while two hit their goal infrequently (36% and 11% respectively). Figure 4.3 illustrates the mean heart rate for each intervention participant taken every 10 minutes throughout the hour - long class. The pattern of response shows an increase in HR during the first 30 minutes of the class that corresponds to the aerobic exercise component. Some participants' heart rate increase was greater than others, which was directly related to the effort (intensity)

put into the exercise. Anecdotally, participants' level of effort did not change much over the course of the program; those that exerted themselves at the start did so consistently to the end of the 6-month program and the same for those who did not exert a great deal of effort.

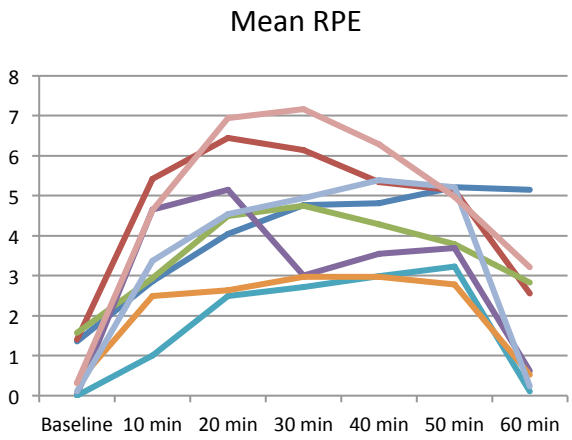
Figure 4.3 Intervention Mean Heart Rate



The PI used the 'talk test' method to monitor participant exercise intensity during the classes. Persons able to talk comfortably in short sentences during exercise are considered to be below the first ventilator threshold (VT_1), the point at which ventilation rates increase to expel carbon dioxide resulting from buffering lactic acid (American Council on Exercise, 2010). VT_1 approximates the study's target rating of perceived exertion (RPE) of 3 to 4 on the 0 to 10 Borg RPE scale (American Council on Exercise, 2010; Borg, 1998). Participants exercising at higher intensity spoke much less and in short one- or two-word sentences than participants exercising at lower intensity who spoke a great deal. One participant had a consistently high heart rate upon arrival to the YMCA. Her resting heart rate was 78 and her mean baseline heart rate was 110.63±12.36. The PI interrupted the aerobic exercise sessions a number of times when

her heart rate exceeded 90% HRR to get the participant to 'take it easy.' Assessment of the participant at the time noted that she was smiling, able to talk albeit in one or two words, and feeling 'good.' Upon further investigation, the participant reported taking a prescription stimulant for fatigue, which would explain the elevated heart rate. The PI monitored the participant's heart rate continuously throughout the exercise session by observing the signal from the Polar® chest strap, which was displayed on the cardio equipment.

Figure 4.4 Intervention Mean Ratings of Perceived Exertion

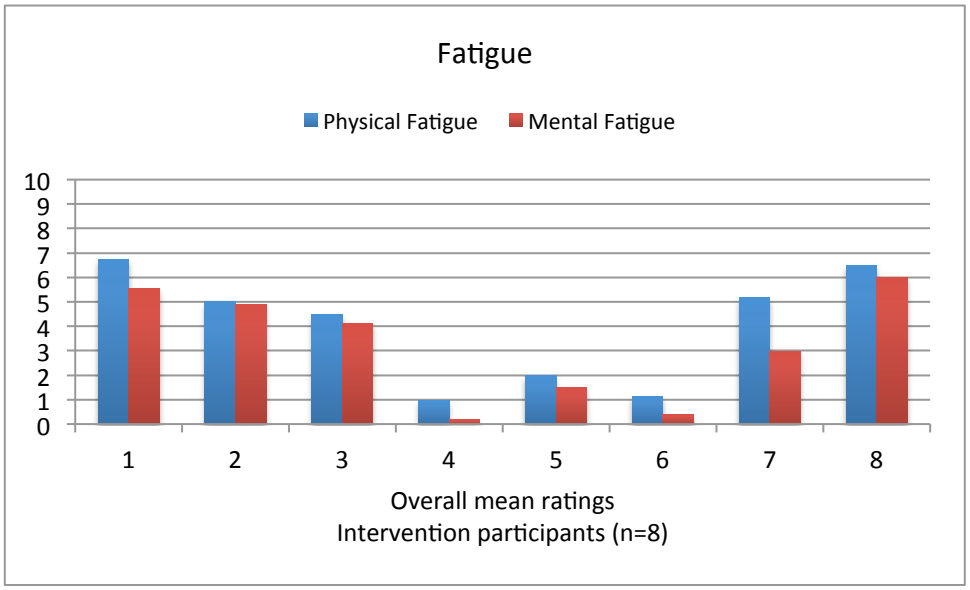


Six of the eight participants attained the targeted goal RPE (from 3 to 7 on the 10-point scale) at every class (Borg, 1998). The other two achieved their goal (92% and 96%). Most of the time participants reported RPE levels above 3 even though their heart rate did not reflect a corresponding increase. Two participants were notable in this regard. One participant with Primary Progressive MS told the PI that he needed to conserve energy to get through the day. His RPE peaked around 20-minutes, which the PI interpreted as the point where he decided he had pushed himself enough for the day. A second participant whose heart rate remained low throughout the class reported extreme

fatigue (clearly apparent to the PI) at baseline and displayed a rising RPE pattern, which did not decrease after 5 minutes of cool down and stretching at the end of the class.

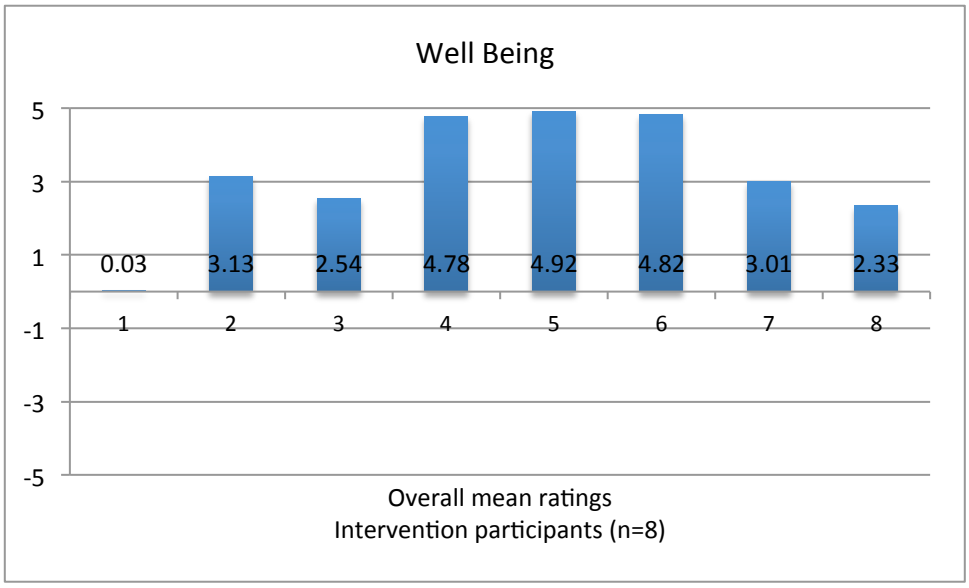
At the end of every exercise class, participants were shown diagrams and asked to use them to rate their (1) mental and physical fatigue on a scale from 0 (no mental/physical fatigue) to 10 (strongest feelings of mental/physical fatigue ever felt); (2) general well being on a scale from +5 (very good) to -5 (very bad); and (3) their level of enjoyment on a scale from 1 (not at all) to 7 (very much) to assess their response to the intervention. Figures 4.5 - 4.6 show overall mean ratings for individual participants rather than for the total group. Numbers on the horizontal axes correspond to the same participant in each figure. Individual participant ratings of fatigue (physical and mental), well being, and enjoyment are displayed in Appendix E.

Figure 4.5 Individual Post-Class Mean Fatigue



Mean physical fatigue rating for the total group was 3.99 ± 2.33, ranging from 0.97 to 6.73 on the 0 to 10-scale (higher ratings indicate higher levels of physical fatigue). Mean mental fatigue rating for the total group on the same scale was 3.20 ± 2.30, ranging from 0.39 to 5.54. Figure 4.5 shows that there was a great deal of variance in mean ratings of physical and mental fatigue among the participants in the intervention group.

Figure 4.6 Individual Post-Class Mean Well Being



Total group ratings of general well being had a mean score of 3.19 ± 1.66, and ranged from 0.03 to 4.92 on the +5 to -5 scale. Positive scores indicated feeling *good*, negative scores indicated feeling *bad*, and 0 indicated a *neutral* feeling. None of the participants reported feeling bad after the class. The participant with the lowest well being mean score (0.03±1.5) attended 38 of the 52 classes. Despite frequent comments to the PI about parathesias (e.g., tingling sensations, pins and needles) involving her right chest wall, leg and foot and significant fatigue most days, the participant reported enjoying the class 'very much' after every class (7.0±0.0). Notably, four months into the

intervention, she applied for, and got, a part-time job. This was the first time in seven years she had sought employment.

Total group mean rating of enjoyment was 6.38 ± 0.85, ranging from 4.8 (somewhat) to 7.0 (very much). As can be seen in Figure 4.7, there was very little variation in responses to the question "How much did you enjoy your exercise session today". The PI did not probe further about the source of enjoyment. Participants may have interpreted the question more broadly than 'doing the exercises' to include the friendly ambiance of the YMCA, the one-on-one attention from the PI, or the sense of personal satisfaction derived from completing the exercise session.

Figure 4.7 Individual Post-Class Mean Enjoyment

EFFECTS OF THE PALMS STUDY

RQ 2.

What are the effects of the PALMS intervention?

RQ 2.1.

What are the within groups, between-groups, and group-by-time interaction effects on the primary outcomes of clinical cognitive function (California Verbal Learning Test [CVLT] Brief Visuospatial Memory Test [BVMT], Controlled Oral Word Association Test [COWAT], the NIH Toolbox Flanker Inhibitory Control and Attention Test, and the NIH Toolbox Oral Symbol Digit Test), self-reported cognitive abilities and concerns (PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales), and neurocognitive function in everyday life (revised Everyday Problems Test [EPT-R] (Benedict, 1997; Benton et al., 1994; Cella et al., 2007; Delis et al., 2000; Weintraub et al., 2013; Willis et al., 1992)?

Primary outcome data were examined for outliers and violations of the assumptions required for conducting a two-way mixed analyses of variance (ANOVA): normality, homogeneity of variance, homogeneity of covariance, and sphericity (Table 4.4). There were three outliers, as assessed by boxplot, but none as assessed by studentized residuals. The data were normally distributed, as assessed by Shapiro-Wilk's test of normality (p>.05). Levene's test of homogeneity of variance was not met (p>.05) for BVMT-total, COWAT, and EPT-R, while the assumption of homogeneity of covariance, as assessed by Box's M test, was met for all variables (p>.05). Mauchley's test of sphericity indicated that the assumption of sphericity was violated for the two-way interactions in: BVMT-delayed, $X^2(2) = 7.009$, p=.030; Flanker, $X^2(2) = 11.290$, p=.004; PROMIS-concerns, $X^2(2) = 6.104$, p=.047; and PROMIS-abilities, $X^2(2) = 10.666$, p=.005; but the assumption was met in: BVMT-total, $X^2(2) = 2.826$, p=.243; CVLT-total,

$X^2(2) = .617$, p=.734; CVLT-delayed, $X^2(2) = .012$, p=.994; COWAT, $X^2(2) = .889$, p=.641; and OSD $X^2(2) = 1.326$, p=.515.

Outlying values were located in the original data collection instrument (e.g., questionnaire) to confirm that the value had been entered correctly. The analyses proceeded as planned without deleting cases or transformations. Unfortunately, there is not a nonparametric alternative to the two-way mixed ANOVA and transformation of variables "are not universally recommended" and "are sometimes harder to interpret" (Tabachnick & Fidell, 2013, p. 86).

Table 4.4 Primary Outcome Variables - Outliers and Assumptions

Instrument	Outliers: Box Plots	Outliers: Studentized Residuals +/- 3 SD	Sharpiro-Wilkes Test of Normality	Levene's Homogeneity of Variance	Box's Homogeneity of Covariances	Mauchley's Test of Sphericity
BVMT-total			Yes	*No*	Yes	Yes
BVMT-delayed			Yes	Yes	Yes	*No*
CVLT-total			Yes	Yes	Yes	Yes
CVLT-delayed			Yes	Yes	Yes	Yes
COWAT	*116-T2*		Yes	*No*	Yes	Yes
Flanker			Yes	Yes	Yes	*No*
OSD			Yes	Yes	Yes	Yes
EPT-R			Yes	*No*	Yes	Yes
PROMIS-concerns	*103-T2*		*No*	Yes	Yes	*No*
PROMIS-abilities	*111-T1*		Yes	Yes	Yes	*No*

BVMT, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test; Flanker, Flanker Inhibitory Control and Attention Test; OSD, Oral Symbol Digit Test; PROMIS-abilities, PROMIS Cognitive Abilities; PROMIS-concerns, PROMIS Cognitive Concerns; EPT-R, Everyday Problems Test-Revised

There were no statistically significant interactions between group and time on any of the primary outcome variables (see Table 4.5). The main group effect showed that there were no statistically significant differences between groups. The main effect of time was significant for CVLT-total, COWAT, OSD, and PROMIS-concerns, while not significant for BVMT-total, BVMT-delayed, CVLT-delayed, Flanker, EPT-R and PROMIS-abilities.

Effect size, a reflection of practical significance, was reported in the SPSS output as partial eta squared. Partial eta squared in this two-way mixed ANOVA is interpreted as the proportion of variance in the dependent variable that is predicted by the level of the independent variable (time, group, and their interaction) after variance attributable to using the same subjects has been removed (Tabachnick & Fidell, 2013; Warner, 2013). Partial eta squared is computed by dividing the sum of squares for the treatment (e.g., group, time, or their interaction) by the sum of the sum of squares for the treatment plus the sum of squares for the error term:

$$\text{Partial } \eta^2 = SS_{treatment}/(SS_{treatment} + SS_{error)} \qquad \text{(Warner, 2013, p. 991)}$$

The repeated-measures design allows individual differences that do not vary to be partialled out from the error term because the same subjects are used resulting in better statistical power compared to when different subjects are used (i.e., two-way ANOVA). Cohen (1988) offers guidance for cautiously interpreting the size of eta squared: small effect (η^2= .01), medium effect (η^2 = .09), and large effect (η^2 = .25). While none of the interaction effects among the primary outcomes were statistically significant, effect sizes usable in future studies were obtained. PROMIS-cognitive concerns had a medium effect size (η^2 = .114) associated with the interaction effect; CVLT-total, CVLT-delayed,

COWAT, Flanker, OSD, EPT-R and PROMIS-cognitive abilities had small effect sizes (η^2 = .016 to .073); BVMT-total, BVMT-delayed were trivial (η^2 = .005 and .003 respectively). There were also a number of moderate effects associated with the change over time for both groups and large effects for cognitive concerns, COWAT, and the OSD.

Post-hoc pairwise comparisons for the total sample that had significant main effects for time indicate several statistically significant mean differences among the primary variables: CVLT-total, T2:T3, *p*=.023; OSD, T1:T2, *p*=.011 and T1:T3, *p*=.010; PROMIS-concerns, T1:T2, *p*=.038 and T1:T3, *p*=.029; PROMIS-abilities, T1:T3, *p*=.022 (means/standard deviations displayed in Table 4.6).

Figure 4.8 Significant primary outcome pairwise comparisons

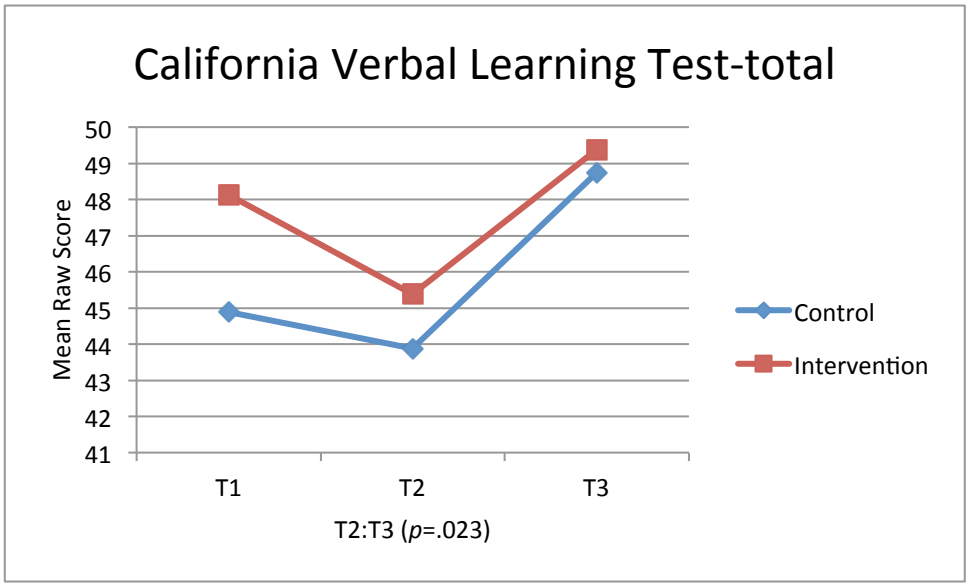
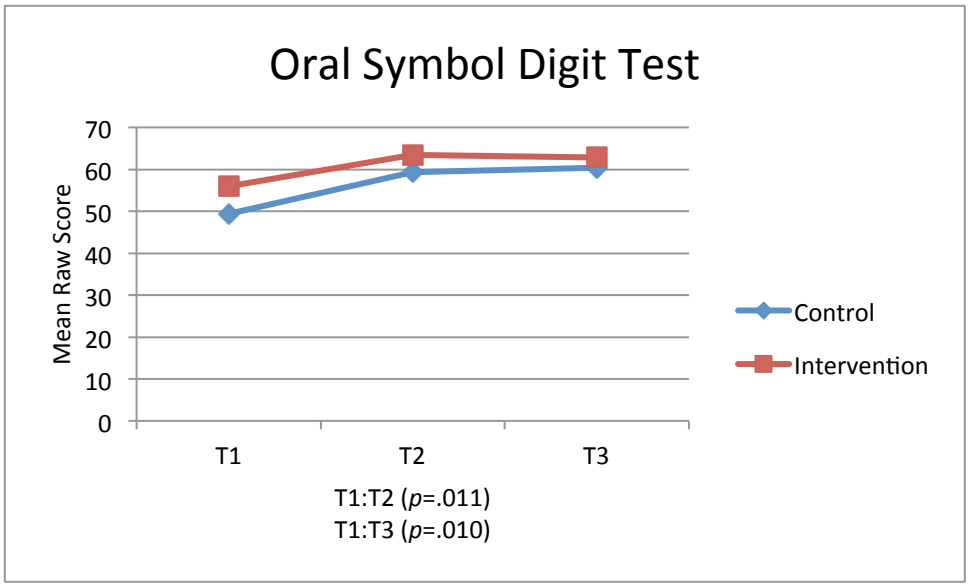


Figure 4.8 Significant primary outcome pairwise comparisons (continued)



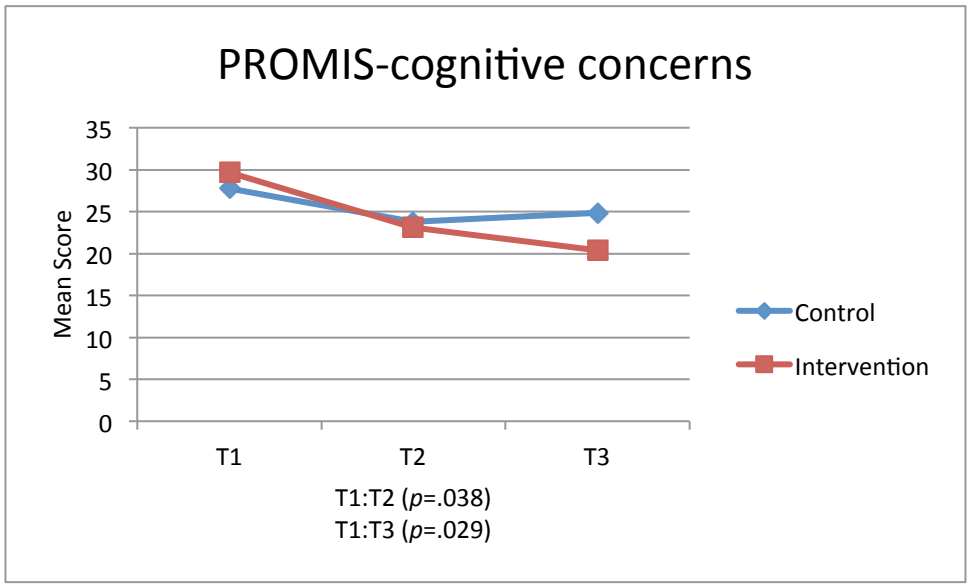


Figure 4.8 Significant primary outcome pairwise comparisons (continued)

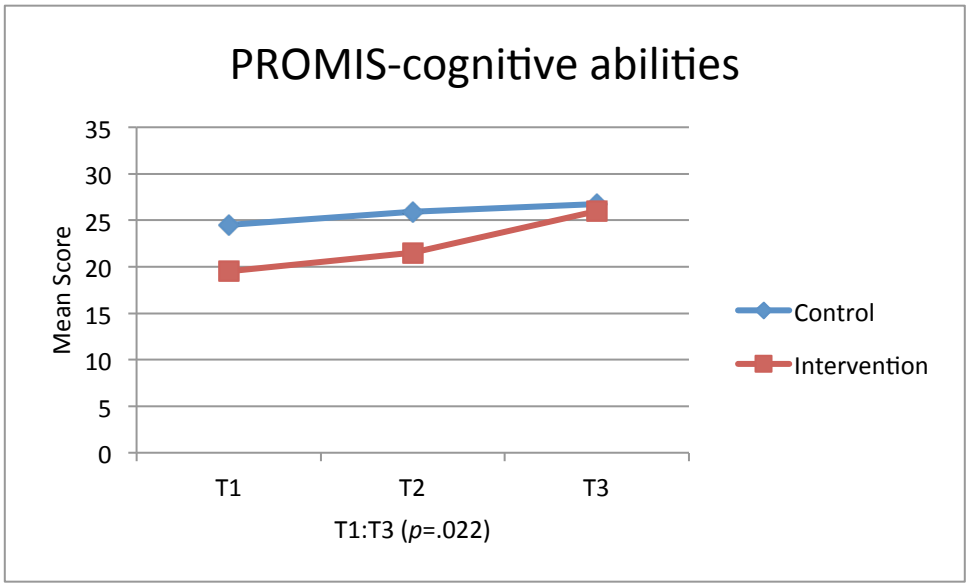


Table 4.5 Primary Outcome Variables - Two way Mixed ANOVA

Instrument	Interaction effect	Main Effect of Group	Main effect of Time
BVMT-total	$F(2, 28) = .066$, $p = .936$, partial $\eta^2 = .005$	$F(1, 14) = .159$, $p = .696$, partial $\eta^2 = .011$	$F(2, 28) = .085$, $p = .919$, partial $\eta^2 = .006$
BVMT-delayed	$F(2, 28) = .043$, $p = .909$, partial $\eta^2 = .003$	$F(1, 14) = .423$, $p = .526$, partial $\eta^2 = .029$	$F(2, 28) = .821$, $p = .416$, partial $\eta^2 = .055$
CVLT-total	$F(2, 28) = .402$ $p = .673$, partial $\eta^2 = .028$	$F(1, 14) = .056$, $p = .817$, partial $\eta^2 = .004$	$F(2, 28) = 4.462$, $p = .021^{*}$, partial $\eta^2 = .242$
CVLT-delayed	$F(2, 28) = .232$ $p = .794$, partial $\eta^2 = .016$	$F(1, 14) = .192$, $p = .668$, partial $\eta^2 = .014$	$F(2, 28) = 1.197$, $p = .317$, partial $\eta^2 = .079$
COWAT	$F(2, 28) = .862$ $p = .433$, partial $\eta^2 = .058$	$F(1, 14) = 1.695$, $p = .214$, partial $\eta^2 = .108$	$F(2, 28) = 4.710$, $p = .017^{*}$, partial $\eta^2 = .252$
Flanker	$F(2, 28) = .654$ $p = .465$, partial $\eta^2 = .045$	$F(1, 14) = .101$, $p = .755$, partial $\eta^2 = .007$	$F(2, 28) = 2.931$, $p = .097$, partial $\eta^2 = .173$
OSD	$F(2, 28) = .362$ $p = .699$, partial $\eta^2 = .025$	$F(1, 14) = .220$, $p = .647$, partial $\eta^2 = .015$	$F(2, 28) = 9.467$, $p = .001^{***}$, partial $\eta^2 = .403$
EPT-R	$F(2, 28) = .489$, $p = .618$, partial $\eta^2 = .034$	$F(1, 14) = .247$, $p = .627$, partial $\eta^2 = .017$	$F(2, 28) = 2.495$, $p = .101$, partial $\eta^2 = .151$
PROMIS-concerns	$F(2, 28) = 1.796$, $p = .196$, partial $\eta^2 = .114$	$F(1, 14) = .153$, $p = .702$, partial $\eta^2 = .011$	$F(2, 28) = 7.538$, $p = .007^{**}$, partial $\eta^2 = .350$
PROMIS-abilities	$F(2, 28) = 1.100$, $p = .326$, partial $\eta^2 = .073$	$F(1, 14) = 1.421$, $p = .253$, partial $\eta^2 = .092$	$F(2, 28) = 4.010$, $p = .052$, partial $\eta^2 = .223$

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

BVMT, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test; Flanker, Flanker Inhibitory Control and Attention Test; OSD, Oral Symbol Digit Test; PROMIS-abilities, PROMIS Cognitive Abilities; PROMIS-concerns, PROMIS Cognitive Concerns; EPT-R, Everyday Problems Test-Revised

Table 4.6 Primary Outcome Variables - Means and Standard Deviations

	N	Time 1 T1 Mean (SD)	Time 2 T2 Mean (SD)	Time 3 T3 Mean (SD)
BVMT-total				
Control	8	18.5 (9.12)	19 (8.09)	18.88 (8.89)
Intervention	8	20.25 (6.78)	20.5 (4.66)	19.88 (6.53)
Total	16	19.38 (7.81)	19.75 (6.42)	19.38 (7.55)
BVMT-delay				
Control	8	6.63 (2.56)	7.38 (3.25)	7.00 (3.30)
Intervention	8	7.63 (3.07)	8.13 (2.42)	7.75 (1.98)
Total	16	7.13 (2.78)	7.75 (2.79)	7.38 (2.66)
CVLT-total				
Control	8	44.88 (19.21)	43.88 (15.42)	48.75 (18.26)
Intervention	8	48.13 (15.32)	45.38 (11.17)	49.38 (12.43)
Total	16	46.50 (16.78)	44.63 (13.03)	49.063 (15.09)
CVLT-delay				
Control	8	8.63 (3.58)	8.63 (5.29)	9.63 (4.60)
Intervention	8	9.88 (3.76)	9.50 (3.66)	10.13 (3.98)
Total	16	9.25 (3.61)	9.06 (4.42)	9.88 (4.16)
COWAT				
Control	8	27.75 (12.49)	29.50 (14.63)	31.50 (14.79)
Intervention	8	33.50 (9.46)	38.88 (8.87)	38.00 (6.85)
Total	16	30.63 (11.10)	34.19 (12.65)	34.75 (11.63)
Flanker				
Control	8	7.74 (1.07)	8.20 (0.56)	8.31 (0.45)
Intervention	8	7.84 (1.06)	8.02 (0.73)	8.03 (0.90)
Total	16	7.79 (1.03)	8.11 (0.64)	8.17 (0.70)
OSD				
Control	8	49.38 (17.37)	59.25 (24.59)	60.38 (18.88)
Intervention	8	55.88 (15.30)	63.50 (19.14)	62.88 (21.12)
Total	16	52.63 (16.17)	61.38 (21.40)	61.63 (19.39)
PROMIS-abilities				
Control	8	24.50 (7.54)	25.94 (4.07)	26.75 (5.70)
Intervention	8	19.50 (9.20)	21.50 (6.65)	26.00 (6.12)
Total	16	22.00 (8.52)	23.72 (5.80)	26.38 (5.73)
PROMIS-concerns				
Control	8	27.75 (7.72)	23.75 (6.80)	24.88 (5.54)
Intervention	8	29.63 (10.65)	23.13 (4.45)	20.38 (2.50)
Total	16	28.69 (9.04)	23.44 (5.56)	22.63 (4.76)
EPT-R				
Control	8	20.50 (7.37)	21.38 (6.82)	21.50 (7.89)
Intervention	8	21.25 (4.43)	22.50 (3.51)	23.75 (2.92)
Total	16	20.88 (5.89)	21.94 (5.27)	22.63 (5.86)

BVMT, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test; Flanker, Flanker Inhibitory Control and Attention Test; OSD, Oral Symbol Digit Test; PROMIS-abilities, PROMIS Cognitive Abilities; PROMIS-concerns, PROMIS Cognitive Concerns; EPT-R, Everyday Problems Test-Revised

RQ 2.2.

What are the within-group, between-groups, and group-by-time interaction effects on the secondary outcomes of exercise self-efficacy [ExSE], physical activity [GLTEQ and accelerometer activity counts: sedentary, light, moderate-to-vigorous physical activity, and steps], depressive symptoms [CES-D], and fatigue [MFIS] (Fisk et al., 1994; Godin & Shepard, 1985; McAuley, 1993; Pearson et al., 2004; Radloff, 1977)?

Secondary outcome data were examined for outliers and violations of the assumptions required for conducting a two-way mixed analyses of variance (ANOVA): normality, homogeneity of variance, homogeneity of covariance, and sphericity (Table 4.7). There were nine outliers among the eight secondary outcome variables, as assessed by boxplot, and three as assessed by studentized residuals. The data were normally distributed for Sedentary PA, Light PA, and MFIS as assessed by Shapiro-Wilk's test of normality (p>.05) but ExSE, GLTEQ, MVPA, Steps, and CES-D violated the assumption of normality. Levene's test of homogeneity of variance was met (p>.05) for all secondary variables except ExSE. The assumption of homogeneity of covariance, as assessed by Box's M test, was met for ExSE, Sedentary PA, Light PA, MVPA, and MFIS (p>.05) but not for GLTEQ, Steps, and CES-D. Mauchley's test of sphericity indicated that the assumption of sphericity was violated for the two-way interactions in: Steps, $X^2(2) = 8.216$, p=.016, but the assumption was met in: ExSE, $X^2(2) = .570$, p=.752; GLTEQ, $X^2(2) = 1.979$, p=.372; Sedentary PA, $X^2(2) = 1.579$, p=.454; Light PA, $X^2(2) = .260$, p=.878; MVPA, $X^2(2) = 3.804$, p=.149; MFIS, $X^2(2) = 5.589$, p=.061; and CES-D, $X^2(2) = 1.060$, p=.589.

As with the primary outcomes, outlying values among the secondary outcomes were located in the original data collection instrument (e.g., questionnaire) to confirm that the value had been entered correctly. Again, the analyses proceeded as planned without deleting cases or transforming the data based on the general robustness of the ANOVA procedure.

Table 4.7 Secondary Outcome Variables - Outliers and Assumptions

Instrument	Outliers: Box Plots	Outliers: Studentized Residuals +/- 3 SD	Sharpiro-Wilkes Test of Normality	Levene's Homogeneity of Variance	Box's Homogeneity of Covariances	Mauchley's Test of Sphericity
ExSE	*103-T2*		*No*	*No*	Yes	Yes
GLTEQ	*102-T2, 113-T1*	*102-T2, 113-T1*	*No*	Yes	*No*	Yes
SedPA	*116-T3*		Yes	Yes	Yes	Yes
LightPA	*103-T3*		Yes	Yes	Yes	Yes
MVPA	*101-T3, 109-T1*		*No*	Yes	Yes	Yes
STEPS	*117-T2*	*117-T2*	*No*	Yes	*No*	*No*
MFIS			Yes	Yes	Yes	Yes
CES-D	*103-T2*		*No*	Yes	*No*	Yes

ExSE, Exercise Self-Efficacy Scale; GLTEQ, Godin Leisure Time Exercise Questionnaire; SedPA, Sedentary Physical Activity; PA, Physical Activity; MVPA, Moderate to Vigorous Physical Activity; MFIS, Modified Fatigue Impact Scale; CES-D, Center for Epidemiologic Studies Depression Scale

There were no statistically significant interactions between group and time among the secondary outcome variables (see Table 4.8). The main group effect showed that there were no statistically significant differences between the intervention and attention-control groups. The main effect of time was significant for MFIS, which had a large effect size ($\eta^2 = .35$). There were no significant time effects among ExSE, GLTEQ, Sedentary PA, Light PA, MVPA, Steps, or CES-D.

Interaction effect sizes for the secondary outcomes are reported here for use in future studies. Sedentary PA, MVPA, MFIS, and CES-D had medium effect sizes (η^2 = .128, .093, .095, and .160 respectively); EXSE, Light PA, and Steps, had small effect sizes (η^2 = .017, .044, and .038 respectively); while GLETQ was trivial (η^2 = .005).

Post-hoc pairwise comparisons for the total sample indicate one statistically significant mean difference among the secondary variables: MFIS, T1:T3, p=.013 (means/standard deviations displayed in Table 4.9).

Figure 4.9 Significant secondary outcome pairwise comparison

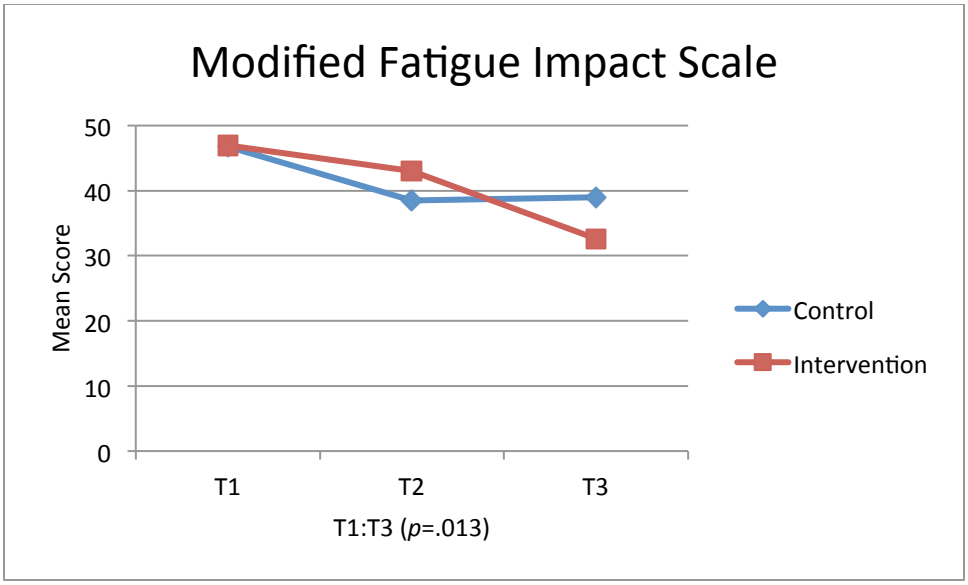


Table 4.8 Secondary Outcome Variables - Two way Mixed ANOVA

Instrument	Interaction effect	Main Effect of Group	Main effect of Time
ExSE	$F(2, 28) = .245$, $p = .784$, partial $\eta^2 = .017$	$F(1, 14) = 1.622$, $p = .224$, partial $\eta^2 = .104$	$F(2, 28) = 1.098$, $p = .348$, partial $\eta^2 = .073$
GLTEQ	$F(2, 28) = .066$, $p = .936$, partial $\eta^2 = .005$	$F(1, 14) = 1.675$, $p = .217$, partial $\eta^2 = .107$	$F(2, 28) = 2.563$, $p = .095$, partial $\eta^2 = .155$
SedPA	$F(2, 28) = 2.062$, $p = .146$, partial $\eta^2 = .128$	$F(1, 14) = 2.258$, $p = .155$, partial $\eta^2 = .139$	$F(2, 28) = .668$, $p = .521$, partial $\eta^2 = .046$
LightPA	$F(2, 28) = .640$, $p = .535$, partial $\eta^2 = .044$	$F(1, 14) = .330$, $p = .575$, partial $\eta^2 = .023$	$F(2, 28) = .694$, $p = .508$, partial $\eta^2 = .047$
MVPA	$F(2, 28) = 1.434$, $p = .255$, partial $\eta^2 = .093$	$F(1, 14) = 1.294$, $p = .274$, partial $\eta^2 = .085$	$F(2, 28) = .681$, $p = .514$, partial $\eta^2 = .046$
STEPS	$F(2, 28) = .559$, $p = .516$, partial $\eta^2 = .038$	$F(1, 14) = .785$, $p = .390$, partial $\eta^2 = .053$	$F(2, 28) = .414$, $p = .590$, partial $\eta^2 = .029$
MFIS	$F(2, 28) = 1.474$, $p = .246$, partial $\eta^2 = .095$	$F(1, 14) = .016$, $p = .902$, partial $\eta^2 = .001$	$F(2, 28) = 6.027$, $p = .007^{**}$, partial $\eta^2 = .301$
CES-D	$F(2, 28) = 2.665$, $p = .087$, partial $\eta^2 = .160$	$F(1, 14) = .356$, $p = .560$, partial $\eta^2 = .025$	$F(2, 28) = 1.068$, $p = .357$, partial $\eta^2 = .071$

*$p<0.05$; **$p<0.01$; ***$p<0.001$.
ExSE, Exercise Self-Efficacy Scale; GLTEQ, Godin Leisure Time Exercise Questionnaire; SedPA, Sedentary Physical Activity; PA, Physical Activity; MVPA, Moderate to Vigorous Physical Activity; MFIS, Modified Fatigue Impact Scale; CES-D, Center for Epidemiologic Studies Depression Scale

Table 4.9 Secondary Outcome Variables - Means and Standard Deviations

		Time 1	Time 2	Time 3
	N	Mean (SD)	Mean (SD)	Mean (SD)
ExSE				
Control	8	7.81 (2.34)	7.13 (2.77)	7.77 (2.13)
Intervention	8	8.63 (1.83)	8.44 (2.72)	9.25 (0.89)
Total	16	8.22 (2.07)	7.78 (2.74)	8.51 (1.75)
GLTEQ				
Control	8	6.00 (3.59)	30.00 (49.13)	18.56 (17.52)
Intervention	8	20.56 (40.13)	39.06 (21.04)	33.94 (22.34)
Total	16	13.28 (28.53)	34.53 (36.81)	26.25 (20.96)
Sedentary PA				
Control	8	551.37 (90.08)	534.78 (61.48)	533.90 (62.69)
Intervention	8	570.13 (81.18)	580.50 (79.44)	614.69 (60.82)
Total	16	560.75 (83.40)	557.64 (72.57)	574.29 (72.81)
Light PA				
Control	8	235.49 (55.22)	231.75 (58.33)	226.58 (70.71)
Intervention	8	225.70 (52.40)	201.02 (54.08)	221.50 (65.92)
Total	16	230.59 (52.25)	216.38 (56.61)	224.04 (66.09)
MVPA				
Control	8	11.93 (10.89)	10.64 (7.82)	13.25 (13.38)
Intervention	8	13.51 (8.41)	21.04 (13.09)	16.66 (11.37)
Total	16	12.72 (9.44)	15.84 (11.72)	14.96 (12.12)
Steps				
Control	8	3808.38 (1204.30)	3769.84 (921.68)	4050.55 (2010.31)
Intervention	8	4022.77 (1105.78)	4733.76 (1680.38)	4328.00 (1323.51)
Total	16	3915.57 (1122.37)	4251.80 (1400.69)	4189.28 (1650.43)
MFIS				
Control	8	46.75 (12.67)	38.50 (8.32)	39.00 (8.19)
Intervention	8	47.00 (15.18)	43.00 (14.79)	32.63 (5.18)
Total	16	46.88 (13.50)	40.75 (11.82)	35.81 (7.40)
CES-D				
Control	8	13.25 (11.18)	12.38 (8.03)	14.75 (9.45)
Intervention	8	19.25 (9.15)	17.00 (11.16)	11.25 (7.15)
Total	16	16.25 (10.34)	14.69 (9.69)	13.00 (8.29)

ExSE, Exercise Self-Efficacy Scale; GLTEQ, Godin Leisure-time Exercise Questionnaire; PA, Physical activity; MVPA, Moderate to Vigorous Physical Activity; Steps, Mean Step Count; MFIS, Modified Fatigue Impact Scale; CES-D, Center for Epidemiologic Studies Depression Scale

Chapter 5: Discussion

Chapter 5 presents a summary and discussion of this dissertation study. Sections of this chapter include a discussion of the study's findings: sample, outcome measures, research questions, and limitations. Implications for nursing practice and public health policy are discussed followed by recommendations for future research.

SUMMARY OF THE STUDY

Cognitive impairment is highly prevalent among persons diagnosed with MS, an immune-mediated neurodegenerative disease affecting approximately 2.3 people worldwide (Chiaravalloti & DeLuca, 2008; MSIF, 2013). The negative impact of MS-related cognitive impairment on those affected is considerable. Moreover, cognitive impairment in persons with MS is under diagnosed, difficult to treat, and little or no effective management therapies exist, including MS disease modifying treatments (Amato et al., 2013; Benedict & Zivadinov, 2011; Chiaravalloti & DeLuca, 2008; Schultheis et al., 2001; Kalmar et al., 2008). Therefore, based on findings among older adults and a growing body of research among persons with MS, management of cognitive impairment through increasing physical activity holds substantial promise and importance (Colcombe & Kramer, 2003; Motl, Gappmaier, et al., 2011; Smith et al., 2010).

The purpose of this study was to determine the feasibility and effects of a physical activity program on measures of clinical cognitive function and neurocognitive function in everyday life in ambulatory persons with MS experiencing cognitive problems. The conceptual framework proposed to guide this study was Alfred Bandura's self-efficacy theory (1997) and social cognitive theory (1986). However, high levels of exercise self-efficacy in both groups at all data collection time points as well as the inability to deliver

the intervention in small groups as intended, made use of the framework less tenable. Slow recruitment of participants into the intervention arm precluded forming small groups, yet YMCA members working out at the same time as the study's participants provided uniquely well-suited role models.

After receiving IRB approval from The University of Texas at Austin, a convenience sample of 16 people with MS confirmed by their healthcare provider; (1) age 21 to 60; (2) able to read and write in English; (3) ambulatory with minimal assistance; and (4) with written approval to participate in the PALMS physical activity program were recruited into the study over an 12-month period. The 16 participants enrolled into the study signed The University of Texas at Austin IRB-approved informed consent document prior to any data being collected.

DISCUSSION

Sample

There was significant demographic diversity among the 16 persons successfully recruited into the study. More males were recruited (5 of the 16 participants) than anticipated, since the proportion of women to men with MS is reported to be 2.3-3.5:1 (Harbo, Gold, & Tintoré, 2013). Only 3 of the 16 participants were Hispanic, while low for an area where 33.5% of the population is Hispanic (U.S. Census Bureau, 2016) it's not surprising given that MS predominates in persons with Caucasian ancestry (Aguirre-Cruz, Flores-Rivera, De La Cruz-Aguilera, Rangel-López, & Corona, 2011). Other demographic variables (e.g., age, marital status, education, employment) were more characteristic of other studies of persons with MS.

Participants' ages averaged 45.6 $\pm$ 9.1 years and ranged from 31 to 58, which was predictable as most people are diagnosed with MS between ages 20 and 50 (NMSS,

2016). More than half were employed (full or part-time), which impeded attendance in both groups. Employment-related absences were less of a problem in the intervention than the attention-control group because the PI accommodated for schedule changes while the attention-control facilitator maintained a Tuesday/Friday 10:30am to 11:30 am schedule throughout the study.

While about half of the sample were married or lived with a significant other, four had never been married and three were divorced or separated. One participant separated from her partner midway through the study but attended 17 intervention classes after the separation until moving to San Antonio. The participant commented that exercising gave her "something to do," relieved stress, and afforded her a therapeutic relationship with the PI.

Functional impairment varied widely among the sample from those with very minimal impairment to those with moderate physical and cognitive function impairment (EDSS 4.5$\pm$1.1, range 2.5 to 6.0). Only one participant routinely used a cane during the study although a few did on occasion especially when feeling "unsteady." The PI discussed the possibility of using an assistive device with several of the participants but almost all reported not wanting to unless they "had to," which is consistent with the literature (Finlayson, Peterson, & Cho, 2006). Cognitive impairment was assessed prior to enrollment using the SDMT (mean 41.7$\pm$10.0, range 20 to 56). The PI and facilitator observed slow "thinking" (processing speed), forgetfulness (memory), and difficulty with organizational skills (executive function) among several participants throughout the study. One participant in his mid-30s was particularly challenged with everyday cognitive function. He stated that he did not work or drive because of his cognitive impairment and had to rely on family members for household task such as bill paying.

There was considerable variation in the type and duration of MS among the participants. One had been diagnosed with primary progressive MS 11 months before enrolling while another had been diagnosed with relapsing-remitting MS for almost 30 years. The recently diagnosed participant heard about the study six-months before contacting the PI, saying that he had to "adjust" to his MS diagnosis as well as accept retiring from work on social security disability insurance (SSDI) before contacting the PI. The participant with *longstanding* MS (Morrison & Stuifbergen, 2014) was also receiving SSDI having retired from full-time employment due to disability but she had had many years to adapt to living with MS.

Outcome Measures

Cognitive Function

There were no significant group-by-time interaction effects or differences between among the seven clinical cognitive function tests employed in this study (BVMT total, BVMT delayed, CVLT total, CVLT delayed, COWAT, Flanker, and OSD) or for the revised Everyday Problems Test. All tests were administered during the same testing session at baseline, T2 and T3. Several significant ($p<.05$) time effects and pairwise comparisons for the total sample (n=16) were found including: improved auditory/verbal learning (CVLT), processing speed (OSD), and self-reported cognitive function ability (PROMIS-cognitive abilities) as well as lower self-reported cognitive function concerns (PROMIS-cognitive concerns)[Figure 4.8]. It is arguable that these significant pairwise comparisons stem from the time spent with and/or attention from the group facilitator or PI, the influence of the control condition (relaxation, stretching/yoga, meditation), or practice effects from repeated testing. Ultimately, evidence is lacking from this small study to demonstrate that increasing physical activity can improve cognitive performance

as measured by these neuropsychological tests compared with the improvement in the attention-control group. The EPT-R has only one form, so any change in scores may be due to *practice effects* related to using the same questions at baseline, T2 and T3. Furthermore, it is uncertain if the clinical neuropsychological tests employed are sensitive to change over time.

Exercise Self-Efficacy

Exercise self-efficacy (ExSE) was very high in both groups at baseline (8.22±2.07), 3-months (7.78±2.74) and 6-months (8.51±1.75) on the 0-10 scale where 10-indicates 100% confidence. It is certainly plausible that high exercise self-efficacy is prerequisite for persons with MS to participate in a twice-weekly exercise program lasting 6 months. Persons with lower levels of exercise self-efficacy may not have had enough confidence in their ability to exercise to even consider participating in a physical activity study, yet these are the individuals most in need and apt to derive the greatest benefits from such a program. The challenge is how to attract persons with low exercise self-confidence to participate in an exercise program designed to meet participants 'where they are' and tailored to build new skills.

There were small, non-significant differences between the two study groups on the ExSE scale at each measurement point (Table 4.9). Mean scores rose slightly in the intervention group from baseline to T3 while the attention-control group remained stable. These improved scores and the smaller standard deviations in the intervention group may reflect additional self-confidence gained from successfully participating in PALMS study and indicate clinical significance. Participants' were noticeably more comfortable and confident exercising at the YMCA as the study progressed. They learned how to use the cardio equipment, how to set up a weight machine, and improved their exercise skills in a

uniquely welcoming and inclusive environment at the YMCA. One participant reported that he 'hated' using the elliptical machine at first but over time, he became proficient and thoroughly enjoyed himself.

Physical Activity

Quantifying physical activity among this small sample of participants proved to be challenging. Participants reported that wearing the ActiGraph® accelerometer on an elastic belt around their hips for 7 days was bothersome. Examination of baseline output from the devices showed that several participants had not worn the ActiGraph® daily as instructed: during waking hours for 7 days. To increase the number of days participants wore the device, the PI sent daily text reminders to participants during T2 and T3 data collection periods, which improved adherence to the protocol (Morrison, Stuifbergen, & Cassill, 2016).

Inspection of data derived from self-report instruments and ActiGraph® devices reveal several interesting patterns. Self-reported physical activity data was categorized as *moderately active* or *active* using Godin's (2011) formulae and the ActiGraph® data was categorized using MS specific cutoffs for moderate-to-vigorous physical activity developed by Sandroff et al. (2012). The tables shown in Appendix F, display data based on (1) USDHHS 1996, 1999 physical activity guidelines for Adults developed by Godin (2011); (2) Canadian physical activity guidelines for persons with MS (2013); and (3) USDHHS physical activity guidelines for adults (2008). Visual inspection of the tables in Appendix F show that the control group reported less *moderately active* and *active* physical activity than the intervention group did at all data collection time points. Self-reported physical activity categorized as *moderately active* and *active* using Godin (2011) criteria appears under-reported compared to ActiGraph® data categorized as meeting

Canadian Physical Activity Guidelines for Persons with MS using Sandroff et al. (2012) criteria. But self-reported physical activity was more comparable to ActiGraph® data categorized as meeting USDHHS physical activity guidelines for adults (2008). Notably, no patterns were discerned at the individual-participant level. While these are rough estimates and do not reflect the recommended twice-weekly strength training criteria in both guidelines, over half of all of the participants in the intervention group met the Canadian guidelines at all data collection time points while few met the more rigorous USDHHS 2008 guidelines.

Depressive Symptoms (CES-D)

Clinically significant depression is common in MS, occurring in over 50% of persons diagnosed with the disease (Feinstein, 2011a). Appendix G shows that while half of the participants had CES-D scores above the cutoff for elevated depressive symptomology at baseline, there were more individuals above the cutoff score in the intervention group (n=6) than in the control group (n=2) (Verdier-Taillefer et al., 2001). Depressive symptoms fell below the cutoff except for one intervention and two control participants at T2. At T3, two intervention and three control participants scored above the cutoff. These fluctuations in depressive symptoms were not unexpected and may reflect usual variance in day-to-day mood.

Two participant's CES-D scores remained above the cutoff at all time points. One, participant 11 (see Appendix G), was the individual who dropped out after only attending two attention-control classes so her baseline score was used at T2 and T3 in this intention-to-treat analysis. The other participant with persistently high depressive symptoms, participant 1 in the intervention group, was the individual who during the intervention applied for, and got, a part time job after 7+ years of unemployment. This

may suggest an increase in self-confidence derived from participating in the PALMS intervention, which allowed her to compensate for her MS symptoms including depressed mood.

Fatigue Impact (MFIS)

Fatigue, the most frequently reported symptom among persons with MS, varied widely among the participants in this study (Minden et al., 2006). Anecdotal reports of fatigue experienced by participants indicated that fatigue contributed to class absences as well as decreased functional performance during intervention classes. Several participants reported being very fatigued before and during the intervention class at different times over the 6-month study. The PI observed outward signs of fatigue (heavy eyelids, slow movement, sighing) in these participants. Mean post-exercise physical and mental fatigue varied widely among the eight intervention participants (see Figure 4.5). As can be seen in Appendix E, individual patterns of physical and mental fatigue reported at the end of each class attended varied over time. Some participants had high ratings of fatigue (participant 1 and 8), some had almost none (participants 4 and 6), some improved (participants 1, 4, and 6), some stayed about the same (participant 2), and others worsened over time (participants 2 and 5) as indicated by the solid trend-line superimposed over the individual ratings in Appendix E.

As was discussed in Chapter 1, symptoms of fatigue and depression in persons with MS overlap, their relationship is equivocal, and both may confound performance on neurocognitive function assessment (Bol et al., 2009; Chadhuri & Behan, 2004; Langdon, 2011; Pierson & Griffith, 2006). Additionally, MS symptoms commonly vary in intensity throughout the day as well as from one day to the next. Fatigue decreased significantly in

both groups, which speaks to the value of both group interventions that involved movement in reduced fatigue.

Research Question 1

What is the feasibility of delivering a small group moderate-intensity exercise program for persons with MS over a 6-month time period?

This study presents several novel insights into the feasibility of delivering a nurse-led community-based physical activity program twice a week for 6 months. Foremost is the ability of community and faith-based organizations (e.g., YMCA, Mt Zion Baptist Church, National MS Society) to successfully collaborate over shared health-promotion goals and provide material support. The YMCA of Austin provided free memberships at six locations in Travis and Hays counties to intervention participants for the 6-months they were in the study. The facilities and the YMCA staff were uniquely well suited to addressing the physical and psychosocial needs of the study participants in a welcoming and inclusive environment. Staff at each site warmly welcomed members (participants) each time they entered the facility reflecting the organization's goal to promote and provide an inclusive environment for the community. Each site was ADA accessible and had equipment available that was specifically designed for use by persons with functional impairment including a recumbent stepper, which allows persons with poor balance to safely exercise both upper and lower extremities. The YMCA's inclusive environment offered unique opportunities for study participants to observe and model their behavior after other YMCA members with disabilities. YMCA members with functional limitations (e.g., stroke, traumatic brain injury, cancer, advanced age, intellectual disability) were warmly welcomed by the YMCA staff and frequently exercised at the same time as this study's participants. Some exercised alone, others with a trainer, and

some in groups. Over the six months of the study, members and participants came to greet as well as encourage each other. Modeling of positive health behaviors by peers with similar, if not greater, physical limitations can have far-reaching effects that may be large and long lasting (Bandura, 1986).

Mt Zion Baptist Church provided accessible classroom space and onsite parking at no charge for the attention-control group twice a week from January 2015 to July 2016. The church has a long history of supporting health promotion programs for its congregation as well as for the community.

The NMSS supported recruiting efforts throughout the study. Community support-group leaders distributed recruiting flyers to their large email network numerous times from November of 2014 to January of 2016. They also welcomed the PI to recruit in-person five times to a large group in north Austin, three times at a smaller central Austin group, and twice to a small group in south Austin. Two groups meet monthly; one in central Austin targeted at persons mildly affected by MS and another in north Austin that meets on Saturday morning for persons with MS as well as their families. A third small group meets weekly at a coffee house in South Austin that is close to where they live and on the bus line. A common topic of conversation at all of these groups is the difficulty of getting to places around Austin as many of them do not drive. Many people on the large email distribution list do not attend meetings because of transportation barriers. Despite all of these efforts and NMSS support, it was difficult to recruit sufficient numbers of participants for this study.

Transportation was a key barrier for interested persons being recruited into the study as well as among those who were successfully enrolled. Two study participants used public transportation to get to their respective study sites. One intervention participant used Austin's Capitol Metro bus transportation system to get to the YMCA. In

fact, the YMCA facility selected was further away from her home but was closer to a bus stop. The other person in the attention-control group coupled two transportation systems to get to the attention-control site: the Capitol Area Rural Transportation System (CARTS) and Austin's Capitol Metro Special Transportation Service (STS) for persons with disabilities. This individual was frequently dropped off or picked up at a time convenient for the driver but either significantly early or late for the class. The time spent commuting between home and the study site as well as making arrangements added up to many hours each week for the participant. Notwithstanding these considerable barriers, the participant was able to attend 33 of 52 classes (63.5%).

An important component of the study's feasibility was the ability to find people qualified to facilitate the attention-control group and conduct the neuropsychological testing. The attention-control facilitator was highly qualified to lead a relaxation and stretching program. She was certified in meditation by the Deepak Chopra Center and has a 200-hour yoga teacher-training certificate. She was also willing to drive to Austin twice a week (50+ miles each time) for over 18 months. Likewise, the study's psychometrist was highly qualified to conduct neuropsychological testing and was available evenings and weekends for the duration of the study.

Feasibility also entails the cost of the study, which took a great deal of time (18 months from IRB approval to completion of data collection) and money to conduct. The attention-control group facilitator and psychometrist were paid significantly less than their usual rate for private lessons or working for a psychologist. Their combined salaries accounted for the largest proportion of the research budget. Travel time and expense was considerable; the PI accumulated over 6,600 miles traveling between the School of Nursing and the five YMCA sites and spent 348 hours conducting intervention classes.

Conducting the intervention in small groups of 3-4 individuals as planned was not feasible. Contributing factors included (1) slow recruitment of participants into the study; (2) use of five different YMCA sites to accommodate participant preference; and (3) participants' work-related availability to attend class. The PI tailored the intervention class time and location to maximize attendance. This strategy was particularly effective for participants who were employed (two worked evening/night shifts) or had family responsibilities such as the participant who was employed fulltime and was the primary caregiver for a multi-generational family with young grandchildren and a mother with early-onset dementia.

Programs such as *Shape Up RI* (www.shapeupri.org) offer creative strategies to promote feasibility in future studies. This statewide exercise and weight loss program is based on promoting teamwork and peer support. The program entails using an online social wellness platform, team competitions and self-reported steps, exercise and weight loss.

RQ 1.2.

What is the attendance pattern across the 6-months for the intervention and attention-control groups?

Attendance was significantly better in the intervention group than the attention-control group ($p<.01$). Several factors may have contributed to the difference including participants were recruited specifically for a physical activity study. All but one initially stated they had strong preference to be in the intervention group but later, at T2 and T3 testing, everyone expressed pleasure with their group assignment. The intervention group was conducted one-on-one and tailored to the participants' availability while the

attention-control group was held on the same two days each week regardless of the participants' availability to attend.

Attendance barriers in this study of physical activity were similar to those previously cited in the literature: facilities too far away, lack of time, lack of transportation (Becker, Stuifbergen, & Sands, 1991). The length of the study was a barrier for some participants related to work (new job or shift), family obligations, and moving away from Austin.

RQ 1.3.

What is the frequency, duration, and mode of physical activity documented in the PALMS physical activity log?

Completing the PALMS physical activity log proved too great a burden for the intervention participants. The PI asked intervention participants to log any physical activity done outside of the intervention classes into a blank calendar that was provided at the first meeting. Participants were asked to bring the calendar with them to subsequent classes to discuss what physical activity they did on their own. The PI ceased asking for formal feedback after the first two participants repeated failed to fill in the log. Instead, the PI opted to ask informal questions during the class time about participants' outside physical activities. The last six intervention participants were equally disinclined to document their physical activity done outside of class. Participants were willing to talk casually during the intervention classes about engaging in occasional physical activities such as walking or riding a bike in their neighborhood and going on outings with their families but no structured pattern of leisure-time physical activity was discerned. The PI informed the participants that their 6-month YMCA membership allowed them to use the

facilities any time the YMCA was open but only two participants took advantage of this option and did so infrequently. Anecdotally, the PI's impression was that the participants considered the 2 hours per week intervention class sufficient exercise.

RQ 1.4.

How do participants respond to the PALMS intervention (heart rate, ratings of perceived exertion, physical and mental fatigue, general wellbeing, and enjoyment)?

A critical component of this study's feasibility was determining whether the participants were able to exercise at a moderate to vigorous intensity level. Heart rate (HR) and rating of perceived exertion (RPE) were monitored every 10 minutes from the start to the end of the 60-minute class to make this determination. Goal RPE (between 3 and 7 on the 10-point scale) and HR (40-60% of heart rate reserve) was achieved at every class by over 90% of the participants. Two participants infrequently achieved their goal HR (36% and 11%) but did meet the RPE goal at each class. One participant reported (participant 1 in Appendix E), and clearly appeared, more fatigue than the others. The other (participant 4 in Appendix E) told the PI that he had only so much energy each day and if he 'over-exerted' himself, he wouldn't be able to accomplish everything he wanted to that day but if he kept his intensity 'in check' he would feel energized and have enough energy for the day.

Every intervention class ended with the PI asking the participant to rate their level of physical fatigue, mental fatigue, general wellbeing and level of enjoyment. Participants rated physical fatigue higher (mean 3.99 $\pm$ 2.33) than mental fatigue (mean 3.20 $\pm$ 2.30). Responses range from 0 (no fatigue) to 10 (strongest feeling of fatigue ever felt) on the

physical and mental fatigue scale. Individually, participants were fairly consistent in their ratings of fatigue from session to session; some regularly reported high levels of fatigue while others reported minimal fatigue (see Appendix E). Participants reported feeling "good" after the exercise classes (mean 3.19 $\pm$ 1.66) using the general well being scale, which ranges from +5 (very good) to 0 (neutral) to -5 (very bad). Ratings of enjoyment at the end of the class sessions were high (mean 6.38 $\pm$ 0.85) on enjoyment scale where 1 = not at all, 4 = somewhat, 7 = very much. In summary, the PALMS intervention was feasible based on immediate post-session participant feedback. Participants reported moderate levels of physical and mental fatigue, positive levels of wellbeing, and decidedly enjoyed the supervised exercise program.

Research Question 2

What are the effects of the PALMS intervention?

While no statistically significant interaction effects were found among the primary or secondary outcome variables investigated, several medium to small effect sizes primarily in self-report measures were established that could be used in future studies.

RQ 2.1.

What are the within groups, between-groups, and group-by-time interaction effects on the primary outcomes of clinical cognitive function (California Verbal Learning Test [CVLT] Brief Visuospatial Memory Test [BVMT], Controlled Oral Word Association Test [COWAT], the NIH Toolbox Flanker Inhibitory Control and Attention Test, and the NIH Toolbox Oral Symbol Digit Test), self-reported cognitive abilities and concerns (PROMIS v1.0 Cognitive Abilities and Cognitive Concerns Scales), and

neurocognitive function in everyday life (revised Everyday Problems Test [EPT-R] (Benedict, 1997; Benton et al., 1994; Cella et al., 2007; Delis et al., 2000; Weintraub et al., 2013; Willis et al., 1992)?

While no significant interaction effects or between group differences were found among the primary outcome variables investigated in this study, several statistically significant ($p<.05$) within group effects were observed for the total sample: CVLT-total, COWAT, OSD, and PROMIS-cognitive concerns. Within group changes reflect change over time within the entire sample of 16 persons with MS. The total sample (N=16) had statistically significant ($p<.05$) improvements in verbal learning (CVLT-total) from T2 to T3 and in processing speed (OSD) from baseline to T2 and T3. While the main effect of time was significant ($p<.05$) for word finding (COWAT), no significant pairwise comparisons were found. These findings may be attributable to the study's small sample size as well as a lack of sensitivity to change over time among these diagnostic neuropsychological tests. There was also a significant time effect for self-reported cognitive concerns for the total group. Statistically significant improvement (reflected by lower scores) was seen from baseline to T2 and T3. The effect of time on self-reported cognitive abilities was not significant ($p=.052$), yet there was a significant pairwise difference from baseline to T3 ($p=.022$). Figure 4.8 shows pairwise comparison graphs for PROMIS-cognitive concerns and abilities, which suggest that the intervention group's improvements, while not statistically significant, do improve and may reflect clinical significance. Ultimately, due to the study's small sample size, great caution must be taken in interpreting these results.

RQ 2.2.

What are the within-group, between-groups, and group-by-time interaction effects on the secondary outcomes of exercise self-efficacy [ExSE], physical activity [GLTEQ and accelerometer activity counts: sedentary, light, moderate-to-vigorous physical activity, and steps], depressive symptoms [CES-D], and fatigue [MFIS] (Fisk et al., 1994; Godin & Shepard, 1985; McAuley, 1993; Pearson et al., 2004; Radloff, 1977)?

No significant interaction effects or between group differences were found among the secondary outcome variables investigated in this study. One significant within group effect was observed for the total sample in fatigue impact (MFIS) ($p<.05$), which had a fairly large effect in both groups (see Figure 4.9). While there were no significant differences between groups, the intervention group did have a larger decrease in fatigue than the control group (see Table 4.9). Ultimately, both the PALMS intervention and attention-control condition (relaxation, stretching/yoga, and meditation) resulted in lower fatigue scores in this small study. The significant time effects observed among the primary and secondary outcomes may have been influenced by the enriched, mentally and socially stimulating environments the participants in both groups were both exposed to throughout the study.

LIMITATIONS

This dissertation study is not without limitations. Initially designed as a randomized clinical trial, the study was revised midway through data collection to a quasi-experimental design due to difficulty recruiting participants. Random assignment of participants was replaced with intentional assignment to balance the size of the intervention and control groups. The final sample of 16 was insufficient in size to achieve

the proposed 80% power. Statistical analysis was limited by the small sample size, which can be seen in large standard deviations among the outcome variables.

Due to the nature of this study, participants could not be blinded to group assignment and those assigned to the attention-control group may have been motivated to be more physically active on their own in addition to their assigned group activity. Furthermore, this convenience sample may not reflect people with MS who do not live in the greater Austin are or have low-exercise self-efficacy, and may be biased towards individuals willing to participate in a research study involving twice weekly exercise classes for six months.

Another limitation of this study is that clinical measures of neurocognitive function, designed to differentiate normal from impaired cognitive functioning, may not reflect day-to-day cognitive function critical to routine activities and roles. Furthermore, the neurocognitive tests used in this study were not specifically designed to measure change in function over time.

Most of the measures used in this study were retrospective self–report instruments that may not accurately reflect the construct of interest. Physical activity measured by accelerometers required the participant to remember to wear a device on their waist/hip during waking hours for 7-days. This performance task was challenging to many of the participants and necessitated initiating a protocol of daily text reminders from the PI.

IMPLICATIONS AND RECOMMENDATIONS

Public Health Policy Implications

Janet Fulton, PhD, the chief of the CDC's Physical Activity and Health Branch recently pointed out that "Adults benefit from any amount of physical activity," which includes persons with disabilities and chronic disabling conditions such as MS (CDC,

2016). Healthy People 2020 include objectives aimed at increasing physical activity for the general public, including persons with disabilities, aimed at maximizing health and quality of life (USDHHS, 2016). The disability and health objectives of Healthy People 2020 cite adding "individuals with disabilities to community-based health promotion efforts" as one of its emerging issues (USDHHS, 2016). Therefore, nursing and public health initiatives must prioritize the inclusion of persons with disabilities into physical activity programming and promote full community participation (NCHPAD, 2014). Strategies such as those outlined by the CDC (2011) and NCHPAD (2014) offer clear guidance for developing inclusive policies and programs aimed at increasing physical activity in adults of all abilities and ages. Key policy strategies include individually tailored, social support programs set in the community and accessible by public transportation.

Implications for developing policies to increase physical activity in persons with MS are manifold. Representatives of the study population must be included from the start in the development, implementation and evaluation of research (e.g., community-based participatory research). Existing community resources that are accessible, inclusive, and affordable (e.g., YMCA) must be leveraged against significant program costs (e.g., staff, training, accessible equipment). Community outreach policies are needed such that people with disabilities understand that they are valued and welcomed rather than stigmatized.

New Zealand's 'Green Prescription' initiative could serve as a model for government-supported public health programming to increase physical activity in at-risk individuals such as those with MS (Swinburn et al., 1998). The 3-month Green Prescription program integrates physical activity promotion into the primary health care system. Managed by New Zealand's Ministry of Health, the program connects patients

referred by their health care provider with local resources that furnish detailed physical activity prescriptions along with crucial health promotion supports (e.g., facilities, social support, educational materials). Benefits of program participation lasting 2-3 years after completion were recently reported (Hamlin et al., 2016). This referral system may reach and motivate persons with low exercise self-efficacy who are unlikely to participate in physical activity programs without the added emphasis of a 'prescription.'

Nursing Implications

Nurses in clinical practice should leverage patient visits as 'teachable moments' to counsel and educate their patients on health promotion and physical activity. Asking patients about their current health promoting practices and providing tailored guidance as well as community resources can make a significant impact on positive behavior change. A wealth of tailored materials and clear physical activity guidelines for adults with MS are available free online from the Canadian Society for Exercise Physiology and Canadian MS Society. Yet a significant gap exists. It is unknown if nurses are aware of this valuable resource. A review of the most current guidelines for MS nurses published by the American Association of Neuroscience Nurses (AANN), the Association of Rehabilitation Nurses (ARN), and the International Organization of Multiple Sclerosis Nurses (IOMSN) revealed that exercise or physical activity were only referred to six times (Thompson & Mauk, 2011). The most explicit nursing implication related to physical activity was to "encourage exercise" as a strategy to manage bowel dysfunction (Thompson & Mauk, 2011, p. 30). This underscores the need to include health promotion strategies, including physical activity, in basic as well as continuing nursing education.

Nurses, who continue to top the Gallup Polls' list of trusted professionals, have a duty to promote healthy behaviors in individuals, families and the community

(http://www.gallup.com/poll/1654/honesty-ethics-professions.aspx). Nurses could opt to gain experience in adaptive fitness by becoming certified through the American College of Sports Medicine (ACSM) in conjunction with the National Center on Health, Physical Activity and Disability (NCHPAD) as an Inclusive Fitness Trainer. There is considerable need for more personal trainers with this specialty certification. A search of the ACSM ProFinder database in September of 2016 revealed 259 ACSM/NCHPAD Certified Inclusive Fitness Trainers. Only 11 were in the state of Texas: 3 in Dallas/Ft Worth, 4 in Houston, 3 in San Antonio, and 1 in Austin (the PI).

Future Research

Studies conducted with larger sample sizes are critical for future studies examining the effect of physical activity on cognitive function in persons with MS. While this study demonstrated that a nurse-led physical activity program integrated with existing community- and faith-based organizations is feasible, future studies need to devise innovative methods to recruit and enroll larger samples.

Future studies might consider incorporating internet-based technology (e.g., Skype, FaceTime) and telephone-based communication to reach more people and minimize program cost, while partnering with existing community- and faith-based resources. Specifically targeting individuals with lower levels of exercise self-efficacy than those enrolled in the current study would allow for growth in this key theoretical construct. Additionally, incorporating small groups, whether in person or virtually, may provide opportunity for role modeling and development of supportive relationships to foster physical activity behavior.

Future studies are also needed to develop physical activity log measures that are more sensitive to reflect meaningful change over time. Important considerations include:

involving the target group from the project's start (CBPR principals) and making the log convenient, easy-to-use, accessible (e.g., large print and icons for an app) and enjoyable.

SUMMARY

This dissertation study of the PALMS intervention provided initial evidence as to the feasibility of a nurse-led community-based physical activity intervention. While this study was underpowered due to its small sample size, effect sizes were observed that may be used in future studies examining the effect of physical activity on cognitive function in persons with MS.

Appendices

APPENDIX A: HUMAN SUBJECTS APPROVAL

OFFICE OF RESEARCH SUPPORT

THE UNIVERSITY OF TEXAS AT AUSTIN

P.O. Box 7426, Austin, Texas 78713 · Mail Code A3200
(512) 471-8871 · FAX (512) 471-8873

FWA # 00002030

Date: 03/18/14

PI: Janet D Morrison

Dept: Nursing

Title: Effects of Physical Activity on Cognition in Persons with MS

Re: IRB Expedited Approval for Protocol Number 2014-02-0031

Dear Janet D Morrison:

In accordance with the Federal Regulations the Institutional Review Board (IRB) reviewed the above referenced research study and found it met the requirements for approval under the Expedited category noted below for the following period of time: 03/18/2014 to 03/17/2015. *Expires 12 a.m. [midnight] of this date.* If the research will be conducted at more than one site, you may initiate research at any site from which you have a letter granting you permission to conduct the research. You should retain a copy of the letter in your files.

Expedited category of approval:

☐ 1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review). (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

☐ 2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children2, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

☐ 3) Prospective collection of biological specimens for research purposes by non-invasive means. Examples:
   (a) Hair and nail clippings in a non-disfiguring manner.
   (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
   (c) Permanent teeth if routine patient care indicates a need for extraction.

(d) Excreta and external secretions (including sweat).
(e) Uncannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.
(f) Placenta removed at delivery.
(g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
(h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
(i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
(j) Sputum collected after saline mist nebulization.

☒ 4) Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications).
Examples:
(a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
(b) Weighing or testing sensory acuity.
(c) Magnetic resonance imaging.
(d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.
(e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

☐ 5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).
Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

☐ 6) Collection of data from voice, video, digital, or image recordings made for research purposes.

☒ 7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.

☒ Use the attached approved informed consent document(s).

☐ You have been granted a Waiver of Documentation of Consent according to 45 CFR 46.117 and/or 21 CFR 56.109(c)(1).

☐ You have been granted a Waiver of Informed Consent according to 45 CFR 46.116(d).

Responsibilities of the Principal Investigator:

1. Report immediately to the IRB any unanticipated problems.

2. Submit for review and approval by the IRB all modifications to the protocol or consent form(s). Ensure the proposed changes in the approved research are not applied without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject. Changes in approved research implemented without IRB review and approval initiated to eliminate apparent immediate hazards to the subject must be promptly reported to the IRB, and will be reviewed under the unanticipated problems policy to determine whether the change was consistent with ensuring the subjects continued welfare.

3. Report any significant findings that become known in the course of the research that might affect the willingness of subjects to continue to participate.

4. Ensure that only persons formally approved by the IRB enroll subjects.

5. Use only a currently approved consent form, if applicable.
   Note: Approval periods are for 12 months or less.

6. Protect the confidentiality of all persons and personally identifiable data, and train your staff and collaborators on policies and procedures for ensuring the privacy and confidentiality of subjects and their information.

7. Submit a Continuing Review Application for continuing review by the IRB. Federal regulations require IRB review of on-going projects no less than once a year a reminder letter will be sent to you two months before your expiration date. If a reminder is not received from Office of Research Support (ORS) about your upcoming continuing review, it is still the primary responsibility of the Principal Investigator not to conduct research activities on or after the expiration date. The Continuing Review Application must be submitted, reviewed and approved, before the expiration date.

8. Upon completion of the research study, a Closure Report must be submitted to the ORS.

9. Include the IRB study number on all future correspondence relating to this protocol.

If you have any questions contact the ORS by phone at (512) 471-8871 or via e-mail at orsc@uts.cc.utexas.edu.

Sincerely,

James P. Wilson

James Wilson, Ph.D.
Institutional Review Board Chair

APPENDIX B: CONSENT FOR PARTICIPATION IN RESEARCH

IRB USE ONLY
Study Number: 2014-02-0031
Approval Date: 03/18/2014
Expires: 03/17/2015
Name of Funding Agency: National Institute of Health (NIH)

Consent for Participation in Research

Title: Effects of Physical Activity on Cognition in Persons with Multiple Sclerosis

Introduction

The purpose of this form is to provide you information that may affect your decision as to whether or not to participate in this research study. The person performing the research will answer any of your questions. Read the information below and ask any questions you might have before deciding whether or not to take part. If you decide to be involved in this study, this form will be used to record your consent.

Purpose of the Study

You have been asked to participate in a research study about the effects of a physical activity program on cognitive function, depressive symptoms, and fatigue in ambulatory persons with multiple sclerosis (MS) experiencing cognitive problems. The purpose of this study is to determine the feasibility and effects of a physical activity program on measures of clinical cognitive functioning, neurocognitive functioning in everyday life, depressive symptoms and fatigue in ambulatory persons with MS experiencing cognitive problems.

What will you be asked to do?

If you agree to participate in this study, you will be asked to:

- Undergo a brief (5-minute) in-person cognitive function test scheduled at your convenience at the The University of Texas at Austin, School of Nursing.
- Based on the results of this test, those eligible to participate will continue with baseline data collection by:
    1. Completing a one-time questionnaire that asks you to provide some background information about yourself (e.g., age, education, etc.) and your MS history (e.g., length of time since diagnosis, symptoms experienced); and
    2. Provide the name and address of your healthcare provider, for them to verify your MS diagnosis and sign a medical clearance for you to participate in a physical activity program.
    3. Be randomly assigned to one of two groups. One group will receive a physical activity program and keep a physical activity log. The other group will receive a relaxation and stretching program.
    4. You will meet twice a week for 50 minutes at one of five YMCA of Austin locations: Town Lake, East, Northwest, Southwest or North, or at The University of Texas at Austin, School of Nursing, for 6-months. You will participate with 2-4 other participants during the study activities.

- In three months and at the end of the study (6 months), you will return to The University of Texas at Austin, School of Nursing to complete the following measurements. This ***will not*** replace one of your bi-weekly physical activities.

    1. Completing surveys asking questions about your level of physical activity, depressive symptoms, fatigue and everyday problems you may encounter;

    2. Completing four cognitive tests often used with persons with MS;

    3. Wearing a watch-like device (accelerometer) for 7 days, starting today, which measures and records your level of activity.

This study will take 6-months to complete. Thirty participants will participate in the study.

This is a research study and, therefore, not intended to provide a medical or therapeutic diagnosis or treatment. The intervention provided in the course of this study is not necessarily equivalent to the standard method of prevention, diagnosis, or treatment of a health condition.

What are the risks involved in this study?

This intervention may involve risks that are currently unforeseeable. Possible risks associated with this study may include physical injury (e.g., falling, tripping) and temporary increases in your MS symptoms (e.g., fatigue, numbness/tingling sensations, foot drop) due to elevated core body temperature that may be related to physical activity or environmental conditions (e.g., summer heat). To minimize risks related to the physical activity intervention, you will be supervised throughout each 50-minute intervention session by the Principal Investigator who is a masters prepared RN, a personal trainer certified by the American Council on Exercise, and an American College of Sports Medicine/National Center on Health, Physical Activity and Disability certified inclusive fitness trainer. To minimize risks related to participation in the relaxation and stretching group, a trained facilitator will oversee each 50-minute session who has received training on basic safety precautions for persons with MS (e.g., clearing the floor of debris). Strategies to minimize increased core body temperature include holding classes in an air-conditioned environment and providing ice water at each class meeting.

You may already have concerns about your cognitive function and this may be a source of distress. You may become upset, frustrated, or experience an increase in feelings (depression, anxiety, and anger) when completing the various cognitive tests. Expected risks also include inconvenience and possible fatigue. To minimize inconvenience, appointments for data collection will be scheduled at a mutually acceptable time. If you become fatigued, you may stop at any time and resume later if you are still willing to participate.

With your permission, your healthcare provider will be notified by letter that you are participating in this study and asked to confirm your diagnosis of MS. If for any reason you become upset by the questions in the questionnaire or during the classes, I will refer you to your healthcare provider and provide additional information on community resources that can help you deal with your concerns.

The risks associated with the study are that you might experience an increase in your feelings (depression, anxiety, and anger). We have provided you a list of counseling services available in the area if you need assistance. It is important that you understand that if you need assistance with the management of your emotions such as medication or counseling, you should talk to your healthcare provider about this. If you say during the study that you have thoughts of harming yourself, the principal investigator, Janet Morrison RN, MSN, will talk with you and contact your healthcare provider. Signing this consent document will give her permission to contact your healthcare provider if that situation should arise.

If you wish to discuss the information above or any other risks you may experience, you may ask questions now or call the Principal Investigator listed on the front page of this form at any time. If you request, the principal investigator will provide you with a list of Austin area Mental Health resources that can offer you support.

What are the possible benefits of this study?

The possible benefits of participation include improvements in physical and cognitive functioning and quality of life after the study. Benefits to society include knowledge about the feasibility and effectiveness of a physical activity intervention on cognitive functioning in a chronic condition (MS) that has a heavy burden for individuals and families.

Do you have to participate?

No, your participation is voluntary. You may decide not to participate at all or, if you start the study, you may withdraw at any time. Withdrawal or refusing to participate will not affect your relationship with The University of Texas at Austin (University) in anyway.

If you would like to participate date, sign, and print your name below. You will receive a copy of this form.

What are the alternatives to participating in this research?

There are few alternate cognitive rehabilitation interventions available for persons with MS. Persons with MS could seek individual treatment with a neuropsychologist or workshop sessions that might be offered by the National MS Society.

Will there be any compensation?

You will not receive any type of payment participating in this study.

What if you are injured because of the study?

The University has no program or plan to provide treatment for research related injury or payment in the event of a medical problem. In the event of a research related injury, please contact the principal investigator.

How will your privacy and confidentiality be protected if you participate in this research study?

Your privacy and the confidentiality of your data will be protected through several rigorously adhered to methods including assigning a unique identification number to you that will be used on all study materials instead of your name. A separate list with names, addresses and contact information and the assigned ID numbers of all participants will be kept on the principal investigator's computer in a password-protected file. Only the principal investigator has access to this password-protected file. The principal investigator will write the assigned record number on the completed questionnaire booklets and place them in the locked data entry filing cabinet. The principal investigator will work with questionnaire booklets that have code numbers not names. All data from participants will be entered into a computer that houses the data under a high-security password interface. The data collected may be made available to other researchers in the future for research purposes not detailed in this consent form. In those cases, the data will contain no identifying information that could identify you to the data or your participation in the study. Participant consent forms and forms containing personal information (Phone Pre-Screening Form, Verification of Multiple Sclerosis Diagnosis, and Physician Approval to Participate in the Physical Activity Program) and the list of names with assigned data record identification number will be destroyed five years after completion of the study.

If it becomes necessary for the Institutional Review Board to review the study records, information that can be linked to you will be protected to the extent permitted by law. Your research records will not be released without your consent unless required by law or a court order.

Whom to contact with questions about the study?

Prior, during or after your participation you can contact the researcher Janet Morrison RN, MSN at 512-965-4023 or send an email to jmorrison@mail.nur.utexas.edu for any questions or if you feel that you have been harmed.

This study has been reviewed and approved by The University Institutional Review Board and the study number is **2014-02-0031.**

Whom to contact with questions concerning your rights as a research participant?

For questions about your rights or any dissatisfaction with any part of this study, you can contact, anonymously if you wish, the Institutional Review Board by phone at (512) 471-8871 or email at orsc@uts.cc.utexas.edu.

Participation

If you agree to participate - date, print, and sign your name on the lines below.

Signature

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____
Printed Name

_____ _____
Signature Date

As a representative of this study, I have explained the purpose, procedures, benefits, and the risks involved in this research study.

_____
Print Name of Person obtaining consent

_____ _____
Signature of Person obtaining consent Date

APPENDIX C: LETTERS OF SUPPORT

FOR YOUTH DEVELOPMENT®
FOR HEALTHY LIVING
FOR SOCIAL RESPONSIBILITY

Janet D. Morrison RN, MSN, MSCN, CPT
Doctoral Student
The University of Texas at Austin
School of Nursing
1710 Red River Street
Austin, TX 78701

RE: The feasibility and effects of a physical activity intervention on cognition in persons with multiple sclerosis

Dear Ms. Morrison,

As the Healthy Living Director at the YMCA of Austin, I extend the full support of our leadership and staff from TownLake, East, Northwest, Southwest and North Austin YMCA's to conduct your proposed study on the feasibility and effects of a physical activity intervention on cognition in persons with multiple sclerosis. Our support includes 6 months of access at no cost for you and 25 study participants. These YMCA facilities offer amenities such as indoor pools, full-court gymnasiums, cardio and weight training equipment, locker rooms with showers, as well as multi-purpose rooms for aerobics, yoga and other group exercises.

Your study is an excellent fit with the YMCA's mission: building programs for healthy living that promote strong families, character values, community development and understanding. It also compliments existing Healthy Living programs such as our LIVESTRONG at the YMCA, Rx for Healthy Living, and Diabetes Prevention programs and addresses the needs of underserved members of our Austin community - those with chronic disabling medical conditions such as multiple sclerosis.

I look forward to our future collaboration and partnership on this worthy project.

Sincerely,

Mashariki Cannon
Healthy Living Director
YMCA of Austin
1100 W Cesar Chavez
Austin, TX 78703

The Multiple Sclerosis Clinic of Central Texas
A Clinic Without Walls....Maximizing the Level of Medical Care
To Patients with Multiple Sclerosis

Edward J. Fox, M.D. Ph.D.
Executive Director

Lori Mayer
Director Medical Research Services

May, 22, 2013

Janet D. Morrison, RN, MSN, MSCN
Doctoral Student
The University of Texas at Austin
School of Nursing
1710 Red River Street
Austin, TX 78701

RE: The feasibility and effects of a physical activity intervention on cognition in persons with multiple sclerosis

Dear Ms. Morrison,
As the Director of Medical Research Services at the MS Clinic of Central Texas/Central Texas Neurology Consultants, I fully endorse your proposed study concerning the feasibility and effects of a physical activity intervention on cognitive function in persons with MS. Our clinic is fully committed to assisting you with recruitment for your study. The MS Clinic of Central Texas is a well-established neurology practice in Rounce Rock, Texas, located 20 miles north of Austin since 2000.

Cognitive impairment affects approximately 65% of our 1400 patient population seen in our clinic and has a major impact on their employment status, independence, and quality of life. Sadly, there are few therapeutic options available to manage or treat cognitive impairment in persons with MS. Your research offers an innovative approach to improving the lives of our patients by promoting cognitive health and wellness through physical activity. This compliments our core values and the goals of the care we provide at the MS Clinic of Central Texas. We gladly support your research study.

Sincerely,

Lori L. Mayer, RN, MSN, MSCN, CCRP
Director of Medical Research Services

16040 Park Valley Drive, Building B, Suite 100 • Round Rock, TX 78681 • Phone (512) 218-1222• Fax (512) 218-1393

APPENDIX D: FORMS AND INSTRUMENTS

Forms and Instruments Included

Phone Pre-Screening Form

Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (Jamnik et al., 2011)

Verification of Multiple Sclerosis Diagnosis Form

Physical Approval to Participate in the Physical Activity Program Form

PALMS Physical Activity Log

Background Information Sheet

Exercise Self-Efficacy Questionnaire (McAuley, 1993)

Godin Leisure-Time Exercise Questionnaire (Godin & Shepard, 1985)

Center for Epidemiologic Studies Depression Scale – Revised (Radloff, 1977)

Modified Fatigue Impact Scale (Fisk, Pontefract, et al., 1994)

PROMIS Cognitive Abilities Scale (Cella et al., 2007)

PROMIS Cognitive Concerns Scale (Cella et al., 2007)

Controlled Oral Word Association Test (Benton et al., 1994)

PALMS Accelerometry Log

PALMS Intervention Log

Proprietary Tests Not Included

Self-Administered Expanded Disability Status Scale (Bowen et al., 2001; Kurtke, 1993)

Symbol Digit Modalities Test (Smith, 1982)

California Verbal Learning Test (Delis et al., 2000)

Brief Visuospatial Memory Test (Benedict, 1997)

Flanker Inhibitory Control & Attention Test (Weintraub et al., 2013)

Oral Symbol Digit Test (Weintraub et al., 2013)

Everyday Problems Test – Revised (Willis et al., 1992)

Phone Pre-Screening

Name: _____ Date: _____

1. Project Description:
   - Funded by the National Institutes of Health (NIH)
   - For adults, age 21 to 60, living in the greater Austin area with physician-diagnosed MS
   - Meet twice a week on weekdays for 50 minutes of physical activity for 6 months.
   - Be physically inactive, defined as not engaging in regular physical activity - 30 minutes accumulated each day - on more than 2 days per week during the previous 6 months
   - Able to walk independently (may use single-point assistance such as a cane)
   - 6-month time commitment with 3 data collection meetings (base-line, 3-months and 6-months). At the three data collection meetings, you will be given four cognitive function tests that take about 70 minutes to complete and given a questionnaire booklet to complete at home and return by mail in a postage-paid, addressed envelope we provide.
   - Wear an accelerometer (a watch-like device that records activity levels) for 7 days at baseline, 3-months and 6-months and complete a written log of your activities. You will be given instructions on wearing the accelerometer and completing the activity log at the first data collection meeting.
   - Confirmation of your MS diagnosis and medical clearance for you to participate in a physical activity program signed by your healthcare provider.
     - We will provide forms for you to sign and send to your healthcare provider and assist the process while conforming to privacy of health information protections (HIPAA).
   - Participants will be assigned by chance (like the flip of a coin) to be in one of two groups that receive different activities.

2. Does this sound like a program that you would like to participate in?
   Yes: ____ No: _____

3. If so, I need to ask you a few more questions in order to establish your eligibility for the project:
   - What is your date of birth? Day_____ Month _____ Year _____
   - What is your age? _____ (Confirm age 21-60)
   - Are you able to read and write in English?
     Yes: ____ No: _____
   - Are you able to walk independently (about 2 to 3 blocks – with or without using a cane)?
     Yes: ____ No: _____

- Have you had an MS exacerbation (MS symptoms lasting more than 24 hours not related to an infection) in the past 3 months (90 days)?
  Yes: ____ No: _____
- Are you physically inactive? (Defined as not engaging in regular physical activity - 30 minutes accumulated each day - on more than 2 days per week during the previous 6 months)
  Yes: ____ No: _____
- Do you have transportation available to attend data collection meetings and the physical activity program?
  Yes: ____ No: _____

4. Administer PAR-Q+ to explore general health status and comorbid medical conditions
If the participant does not meet any one of the inclusion criteria, thank the participant for their interest in the study explaining that they are not eligible for this study. Ask them if they would like to be contacted about future research activities?
Yes: ____ No: _____

For those who meet the above inclusion criteria:

5. Contact information

- Phone Numbers:
- Best number to call (circle below) Best time to contact: _____

  Home: _____

  Work: _____

  Other: _____
- Email address:

  _____
- Mailing Address:

  _____

  _____

6. Information about your MS

- When were you diagnosed with MS? Date: _____ (want > 6 months)
- Age when you were diagnosed with MS: _____
- Do you know of any medical conditions that you might have that would keep you from participating in this physical activity program? (Pregnant or planning pregnancy, heart disease, lung disease, psychiatric disease – severe depression)
  Yes: ____ No: _____

7. Information about your availability
   - What weekdays and time of day are the most convenient for you to meet for the physical activity program?
     _____
     _____
   - Is there any time/dates that you cannot attend the physical activity program for more than a week or two? (Vacations, holidays)
     _____
     _____

8. Schedule the IN-PERSON meeting at a location preferred by the subject (e.g., School of Nursing, subject's home, public library).
   - This meeting includes:
     - Discussing any questions you may have about the study
     - Signing the informed consent form
     - Completing the Symbols Digit Modalities Test – a brief (5-minute) test of complex scanning and visual tracking.
     - Receiving an accelerometer to wear for 7 days and an activity log
       - Verbal and written instructions on wearing the accelerometer and filling out the activity log.
     - Receiving a questionnaire booklet to take home to complete.
     - Providing you with a postage-paid, addressed envelope to return the accelerometer, accelerometer log, and the questionnaire booklet to us.
     - Obtaining your signed permission for us to contact your healthcare provider to:
       - Confirm your MS diagnosis
       - Sign a medical clearance form for you to participate in a physical activity program.
       - Physician's Name: _____
       - Address: _____
       - Phone: _____
       - Fax: _____

Scheduled In-person meeting:

Date: _____

Time: _____

Special Instructions:

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

SECTION 1 – GENERAL HEALTH			
Please answer each question honestly: YES or NO		**YES**	**NO**
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?		
2.	Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?		
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).		
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?		
5.	Are you currently taking prescribed medications for a chronic medical condition?		
6.	Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physical active. For example, knee, ankle, shoulder or other.		
7.	Has your doctor ever said that you should only do medically supervised physical activity?		

- ✓ If the informant answered NO to questions # 1, 2, 3, 5, 6, & 7 and the only chronic medical condition in question # 4 is MS, return to phone screen question 4b.

- ✓ If the informant answered YES to ONE or more questions above, GO TO SECTION 2.

SECTION 2 – CHRONIC MEDICAL CONDITIONS				
Please answer each question honestly: YES or NO				
1.	Do you have Arthritis, Osteoporosis, or Back Problems?		**YES** If yes, answer questions 1a-1c	**NO** If no, go to question 2
	1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments).		
	1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or		

		spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?		
	1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?		
2.	Do you have Cancer of any kind?		**YES** If yes, answer questions 2a-2b	**NO** If no, go to question 3
	2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?		
	2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?		
3.	Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm		**YES** If yes, answer questions 3a-3e	**NO** If no, go to question 4
	3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medication or other treatments)		
	3b.	Do you have an irregular heartbeat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)		
	3c.	Do you have chronic heart failure?		
	3d.	Do you have a resting blood pressure equal to or greater than 1560/90 mmHg with or without medication (Answer YES if you do not know your resting blood pressure)		
	3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?		
4.	Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes		**YES** If yes, answer questions 4a-4c	**NO** If no, go to question 5
	4a.	Is your blood sugar often above 13.0 mmol/L (Answer YES if you are not sure)		
	4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the		

		sensation in your toes and feet?		
	4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?		
5.	Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)		**YES** If yes, answer questions 4a-5b	**NO** If no, go to question 6
	5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medication or other treatments)		
	5b.	Do you also have back problems affecting nerves or muscles?		
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure		**YES** If yes, answer questions 6a-6d	**NO** If no, go to question 7
	6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medication or other treatments)		
	6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?		
	6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, labored breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?		
	6d.	Has your doctor ever said you have high blood pressure in your blood vessels of your lungs?		
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia		**YES** If yes, answer questions 7a-7c	**NO** If no, go to question 8
	7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medication or other treatments)		
	7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness,		

		and/or fainting?		
	7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?		
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event		**YES** If yes, answer questions 8a-8c	**NO** If no, go to question 9
	8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medication or other treatments)		
	8b.	Do you have any impairment in walking or mobility?		
	8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?		
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?		**YES** If yes, answer questions 9a-9c	**NO**
	9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?		
	9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?		
	9c.	Do you currently live with two chronic conditions?		

- ✓ If the informant answered NO to all of the follow-up questions about their medical conditions, return to phone screen question 4b.

- ✓ If the informant answered YES to ONE or more of the follow-up questions about their medical conditions **consider excluding them from participating in the study**.

References

Jamnik, V. K., Warburton, D. E., Makarski, J., McKenzie, D. C., Shephard, R. J., Stone, J. A., . . . Gledhill, N. (2011). Enhancing the effectiveness of clearance for physical activity participation: background and overall process. *Applied Physiology, Nutrition, and Metabolism, 36*, S3-13. doi:10.1139/h11-044

Warburton, D. E., Gledhill, N., Jamnik, V. K., Bredin, S. S., McKenzie, D. C., Stone, J., . . . Shephard, R. J. (2011). Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document 2011. *Applied Physiology, Nutrition, and Metabolism, 36*, S266-298. doi:10.1139/h11-062

Verification of Multiple Sclerosis Diagnosis

To the attending physician/neurologist of _____D.O.B.___/___/____

Your patient has expressed interest in participating in a study examining the effects of physical activity on cognitive function in persons with MS. To ensure that we are including individuals with a definite diagnosis of MS, we ask for your assistance in documenting the diagnosis. That is, we ask that you verify that your patient has multiple sclerosis based on standard diagnostic procedures.

Does your patient have a definite diagnosis of MS? Yes _____ No _____

What type of MS was diagnosed?_____

Name (print) _____ Date_____

Signature _____

Thank you for taking the time to read this summary and provide verification of your patient's diagnosis with MS. In order to expedite our scheduling process, please fax this form to the number listed below, and use the provided envelope to return the original for our permanent record. Permission to release information to The University of Texas at Austin, School of Nursing can be found at the bottom of the page.

1. Fax to:
   Janet Morrison RN, MSN
   (512) 471-1571

2. Mail to:
   Janet Morrison RN, MSN
   The University of Texas at Austin
   School of Nursing, RM3.420
   1710 Red River St
   Austin, TX 78701-1499 Campus Mail Code: D0100

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By signing this document I give permission to have my physician fax a verification of MS diagnosis for participation in the study to Janet Morrison at the School of Nursing at The University of Texas at Austin.

Name (print) _____

Signature _____

Date_____

Physician Approval to Participate in the Physical Activity Program

Dear Doctor:

Your patient _____ wishes to take part in a physical activity research study and fitness assessment. The study will involve the following:

- *Type of physical activity*: 10-minute dynamic warm-up, 30-minute aerobic exercise (as tolerated based on Berg Perceived Exertion Scale ≤ 6), 10-minute cool-down.
- *Frequency*: Twice weekly supervised by an RN/Personal Trainer + 30 minutes of physical activity, 3/week at home on own.
- *Duration*: Six months
- *Intensity*: 40 – 60% maximal heart rate

By completing this form, you are not assuming any responsibility for our exercise and assessment program. Please identify any recommendations or restrictions for your patient's fitness program below (Physician's Recommendations).

Patient's Consent and Authorization

I consent to and authorize _____ to release to _____, health information concerning my ability to participate in a physical activity research program and fitness assessment. I understand this consent is revocable except to the extent action has already been taken. Authorization is not valid beyond one year from date of signature. Further disclosure or release of my health information is prohibited without specific written consent of person to whom it pertains.

Participant's signature	Date
Researcher's signature	

Physician's Recommendations

	I am not aware of any contraindications to participation in the physical activity research program.	
	I believe the applicant can participate, but urge caution because:	
	The applicant should not engage in the following activities:	
	I recommend the applicant **not** participate in the above physical activity program.	
Physician's signature		
Physician's name (print)		
Date	Phone	Fax
Address	City	State & Zip

January 2015

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

PALMS PHYSICAL ACTIVITY LOG

1. Record the type of activity you did
Did you go for a walk? Clean house? Garden? All types of physical activity count!

2. Record the time in minutes each day
Write down the number of minutes you were physically active each day.

3. Bring your log to your PALMS session
We will review your log each week

Background Information Sheet

Name _____

Date _____

1. What is your age in years? _____

2. What is your date of birth:

   Month _____ Day _____ Year _____

3. What is your gender:

   Male _____ Female _____

4. What is your race? (Please circle the appropriate answer)
   a. American Indian or Alaska Native
   b. Asian
   c. Black or African American
   d. Native Hawaiian or Other Pacific Islander
   e. White

5. What is your ethnicity?
   a. Hispanic or Latino
   b. Not Hispanic or Latino

6. What is your marital status? (Please circle appropriate answer)
   a. Never been married
   b. Married
   c. Divorced
   d. Widowed
   e. Separated
   f. Living with a significant other

7. How many years of education do you have? _____

Background Information Sheet

8. What is the highest degree you have completed? (Please circle the appropriate answer)
    a. No degree
    b. Vocational Training or Certificate
    c. GED
    d. High School diploma
    e. Associate degree
    f. Bachelors degree
    g. Graduate degree (Masters or Doctoral)

9. What is your current employment status?
    a. I work full-time for pay (Includes farm/ranch work)
    b. I work part-time for pay (Includes farm/ranch work)
    c. I am a full-time homemaker
    d. I am a full-time homemaker and also help with farm/ranch work
    e. I am a full-time homemaker and also work part-time at another job
    f. I am unemployed due to age
    g. I am unemployed due to disability
    h. I am laid off
    i. I have been fired
    j. I am a full-time student
    k. I am a student (full or part-time) and also work for pay
    l. I have been unable to find suitable work because of where I live
    m. I am retired

10. If you are employed, how many hours a week do you work? _____

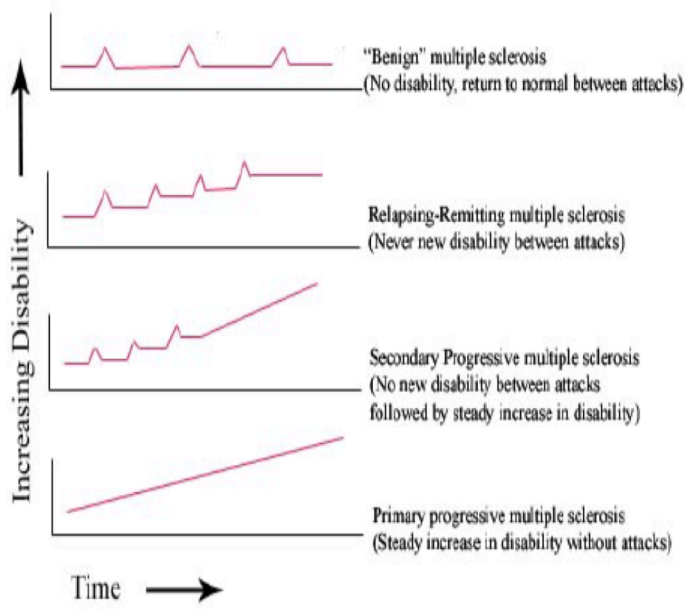
11. Please describe what kind of business or industry you work in:

12. At what age were you diagnosed with MS? _____

13. At what age did you first have symptoms of MS? _____

Background Information Sheet

14. MS tends to take different clinical courses. Which type best describes your experience? (Circle one)

1. Benign 2. Relapsing-Remitting 3.Secondary Progressive 4.Primary Progressive	

Exercise Self-Efficacy Scale

*The items listed below are designed to assess your beliefs in your ability to participate in physical activity on a three time per week basis at moderate intensities, for **20+** minutes per session in the future. Using the scales listed below please indicate how confident you are that you will be able to continue to exercise in the future.*

For example, if you have complete confidence that you could participate in physical activity three times per week at moderate intensity for **20+** minutes for the next four months without quitting, you would **circle 100%**. However, if you had no confidence at all that you could participate in physical activity for the next four months without quitting, you would **circle 0%**.

Please remember to answer honestly and accurately. There are no right or wrong answers.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
NOT AT ALL CONFIDENT				MODERATELY CONFIDENT				HIGHLY CONFIDENT		

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1. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT MONTH.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

2. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT TWO MONTHS.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Mark your answer by circling a %

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
NOT AT ALL CONFIDENT				MODERATELY CONFIDENT				HIGHLY CONFIDENT		

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3. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT THREE MONTHS.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

4. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT FOUR MONTHS.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

5. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT FIVE MONTHS.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

6. I am able to participate in physical activity three times per week at moderate intensity, for 20+ minutes without quitting for the NEXT SIX MONTHS.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross-country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) MODERATE EXERCISE **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) MILD EXERCISE **(MINIMAL EFFORT)** (e.g., yoga, archery, fishing from riverbank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	**SOMETIMES**	**NEVER/RARELY**
(1)	(2)	(3)

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get “going”.	☐	☐	☐	☐

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. If you are not sure which answer to select, please choose the one answer that comes closet to describing you.

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8.	I have been less motived to participate in social activities.	0	1	2	3	4
9.	I have been limited in my ability to do things away from home.	0	1	2	3	4
10.	I have had trouble	0	1	2	3	4

Because of my fatigue during the past 4 weeks…

		Never	Rarely	Sometimes	Often	Almost always
	maintaining physical effort for long periods.					
11.	I have had difficulty making decisions.	0	1	2	3	4
12.	I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13.	My muscles have felt weak.	0	1	2	3	4
14.	I have been physically uncomfortable.	0	1	2	3	4
15.	I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16.	I have had difficulty organizing my thoughts when doing things at home or work.	0	1	2	3	4
17.	I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18.	My thinking has been slowed down.	0	1	2	3	4
19.	I have had trouble concentrating.	0	1	2	3	4
20.	I have limited my physical activities.	0	1	2	3	4
21.	I have needed to rest more often or for longer periods.	0	1	2	3	4

Applied Cognition-Abilities-Short Form 8a

Please respond to each item by marking one box per row.

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. My mind has been as sharp as usual.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. My memory has been as good as usual……....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. My thinking has been as fast as usual……....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. I have been able to keep track of what I am doing, even if I am interrupted.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. I have been able to concentrate.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. I have been able to think clearly without extra effort	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. I have been able to pay attention and keep track of what I am doing without extra effort	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. I have been able to remember things as easily as usual without extra effort…….....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Applied Cognition-General Concerns-Short Form 8a

Please respond to each item by marking one box per row.

In the past 7 days…	Never	Rarely (Once)	Sometimes (Two or three times)	Often (About once a day)	Very often (Several times a day)
1. My thinking has been slow	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. It has seemed like my brain was not working as well as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. I have had to work harder than usual to keep track of what I was doing	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. I have had trouble shifting back and forth between different activities that require thinking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. I have had trouble concentrating	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. I have had to work really hard to pay attention or I would make a mistake	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. I have had trouble forming thoughts	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. My problems with memory, concentration, or making mental mistakes have interfered with the quality of my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

CONTROLLED ORAL WORD ASSOCIATION TEST (test at Baseline)

Name: _____ Date: _____

F	A	S
1	1	1
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6
7	7	7
8	8	8
9	9	9
10	10	10
11	11	11
12	12	12
13	13	13
14	14	14
15	15	15
16	16	16
17	17	17
18	18	18
19	19	19
20	20	20
21	21	21
22	22	22
23	23	23

Sum F: _____ **Sum A: _____** **Sum S: _____**

TOTAL: _____

CONTROLLED ORAL WORD ASSOCIATION TEST (test at T2)

Name: _____ Date: _____

C	F	L
1	1	1
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6
7	7	7
8	8	8
9	9	9
10	10	10
11	11	11
12	12	12
13	13	13
14	14	14
15	15	15
16	16	16
17	17	17
18	18	18
19	19	19
20	20	20
21	21	21
22	22	22
23	23	23

Sum C: _____ **Sum F: _____** **Sum L: _____**

TOTAL: _____

CONTROLLED ORAL WORD ASSOCIATION TEST (test at T3)

Name: _____ Date: _____

P	R	W
1	1	1
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6
7	7	7
8	8	8
9	9	9
10	10	10
11	11	11
12	12	12
13	13	13
14	14	14
15	15	15
16	16	16
17	17	17
18	18	18
19	19	19
20	20	20
21	21	21
22	22	22
23	23	23

Sum P: _____ **Sum R: _____** **Sum W: _____**

TOTAL: _____

PALMS **Accelerometer Log**

Date and time you started wearing the unit: _____/_____

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (month/day)							
Time you got into bed for the night							
Time you turned off the lights to go to sleep							
Time you awoke in the morning							
Time you got out of bed to start your day							
Any time(s)you did not wear the unit? (e.g., naps, bathing, etc.)							

In the space provided below, please provide comments about problems that occurred while you were wearing the unit.

Date: _____ **PALMS INTERVENTION LOG** *ID: _____*

Monitoring								
Phase		Elapsed Time (Minutes)	Heart Rate	RPE Modified Borg	Fatigue		Feeling	Enjoyment
					Physical	Mental		
Baseline		0						
Warm-up		10						
Aerobic exercise	Mode (Circle) Treadmill Stationary Bike Recumbent Bike Elliptical	15						
		20						
		25						
		30						
		35						
		40						
Cool-down		50						

Notes:

PALMS INTERVENTION LOG

Rating of Perceived Exertion (RPE) "How hard do you feel you are working?"	
Modified Borg	**Breathing**
0	No exertion
1	Very light
2	Notice breathing deeper, but still comfortable. Conversation possible.
3	Aware of breathing harder; more difficult to hold conversation
4	
5	Starting to breathe hard and getting uncomfortable
6	
7	Deep and forceful breathing, uncomfortable, don't want to talk
8	
9	Extremely hard
10	Maximum exertion

Feeling Scale "How do you feel right now?"	
+ 5	Very good
+ 4	
+ 3	Good
+ 2	
+ 1	Fairly good
0	Neutral
- 1	Fairly bad
- 2	
- 3	Bad
- 4	
- 5	Very bad

Enjoyment Scale
"How much did you enjoy your exercise session today?"

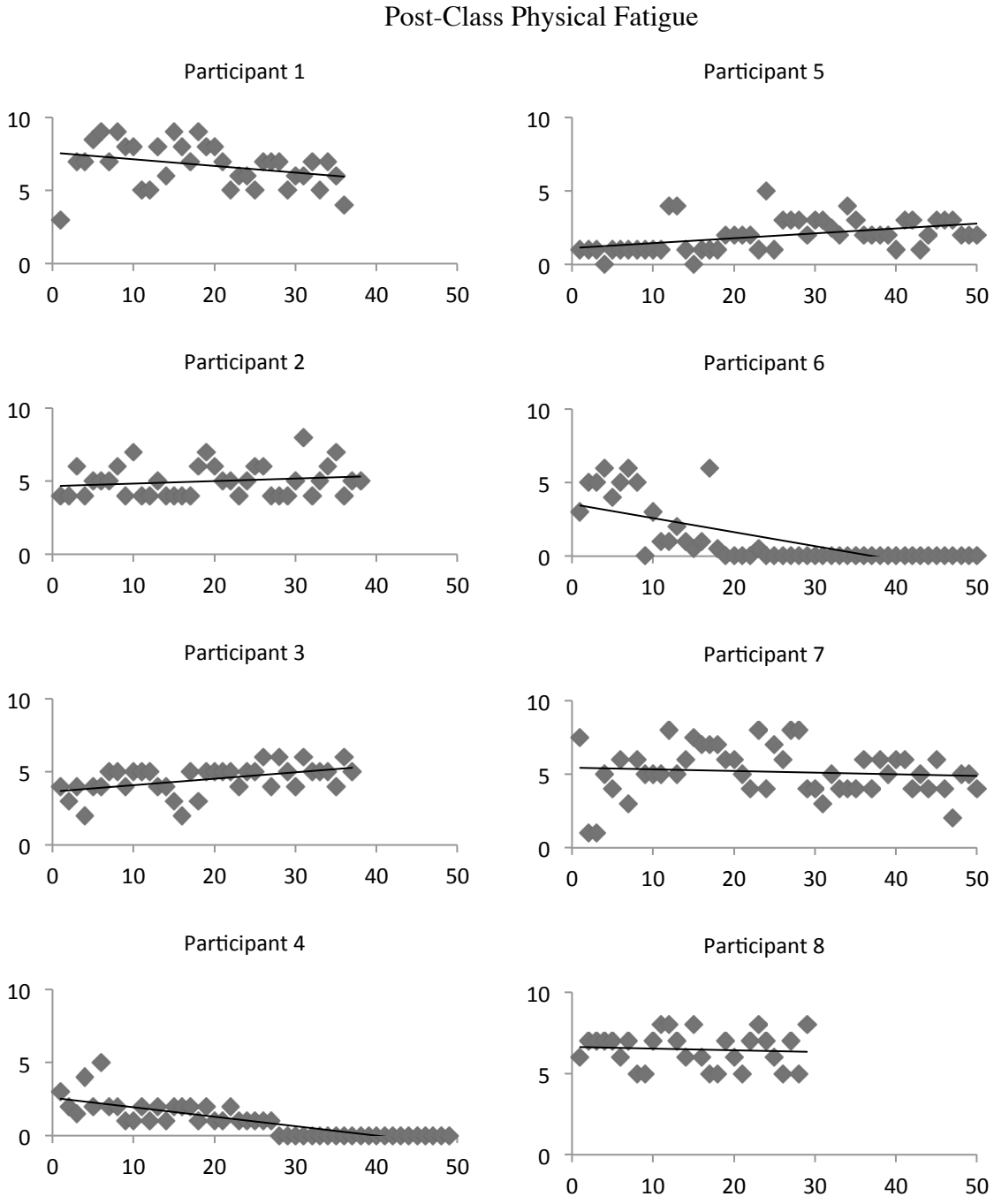
1	2	3	4	5	6	7
Not at all			Somewhat			Very much

Mental and Physical Fatigue Scale

I feel I have no MENTAL/ PHYSICAL Fatigue

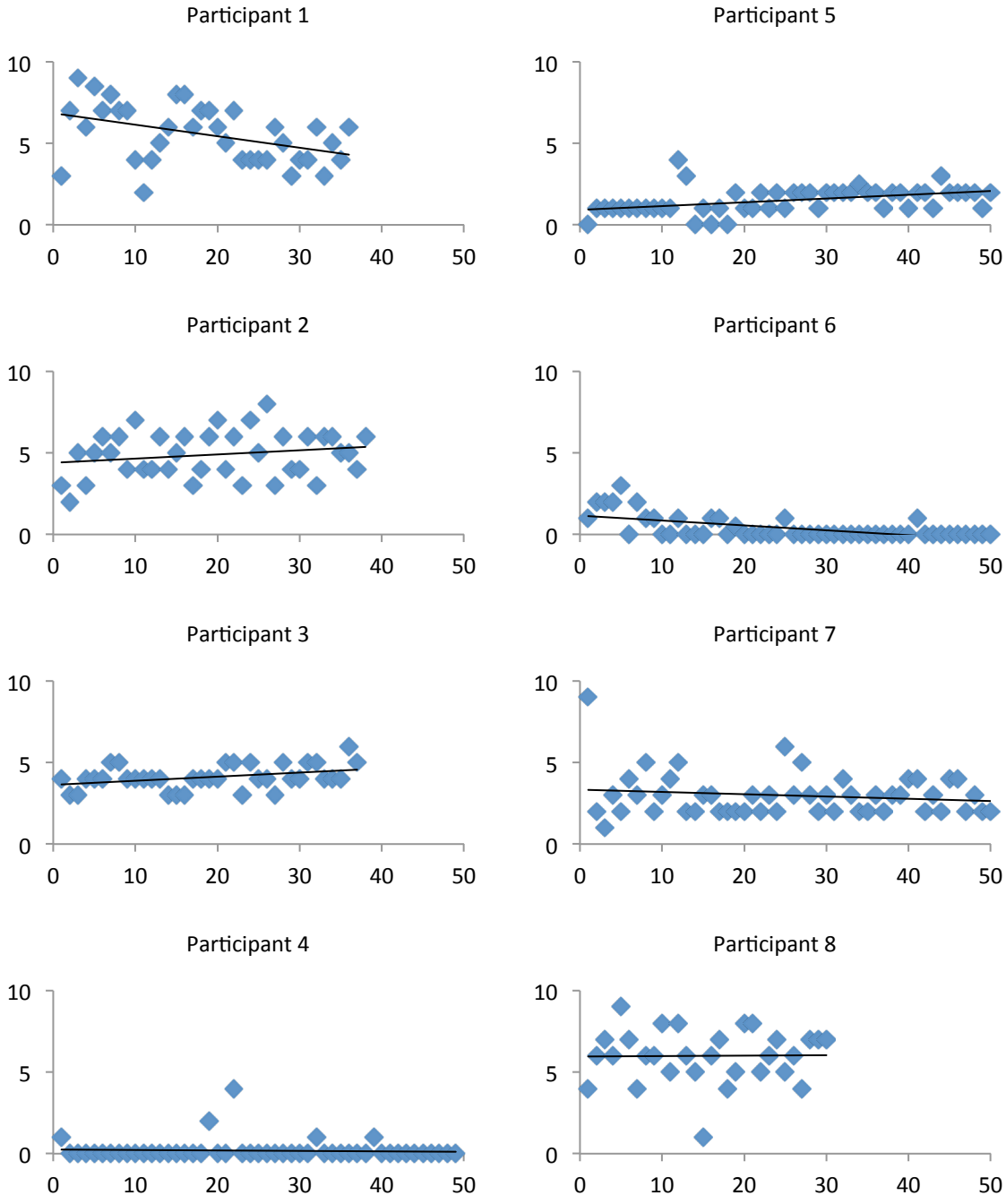
Strongest feelings of MENTAL/ PHYSICAL Fatigue ever felt

APPENDIX E: POST-CLASS ASSESSMENTS



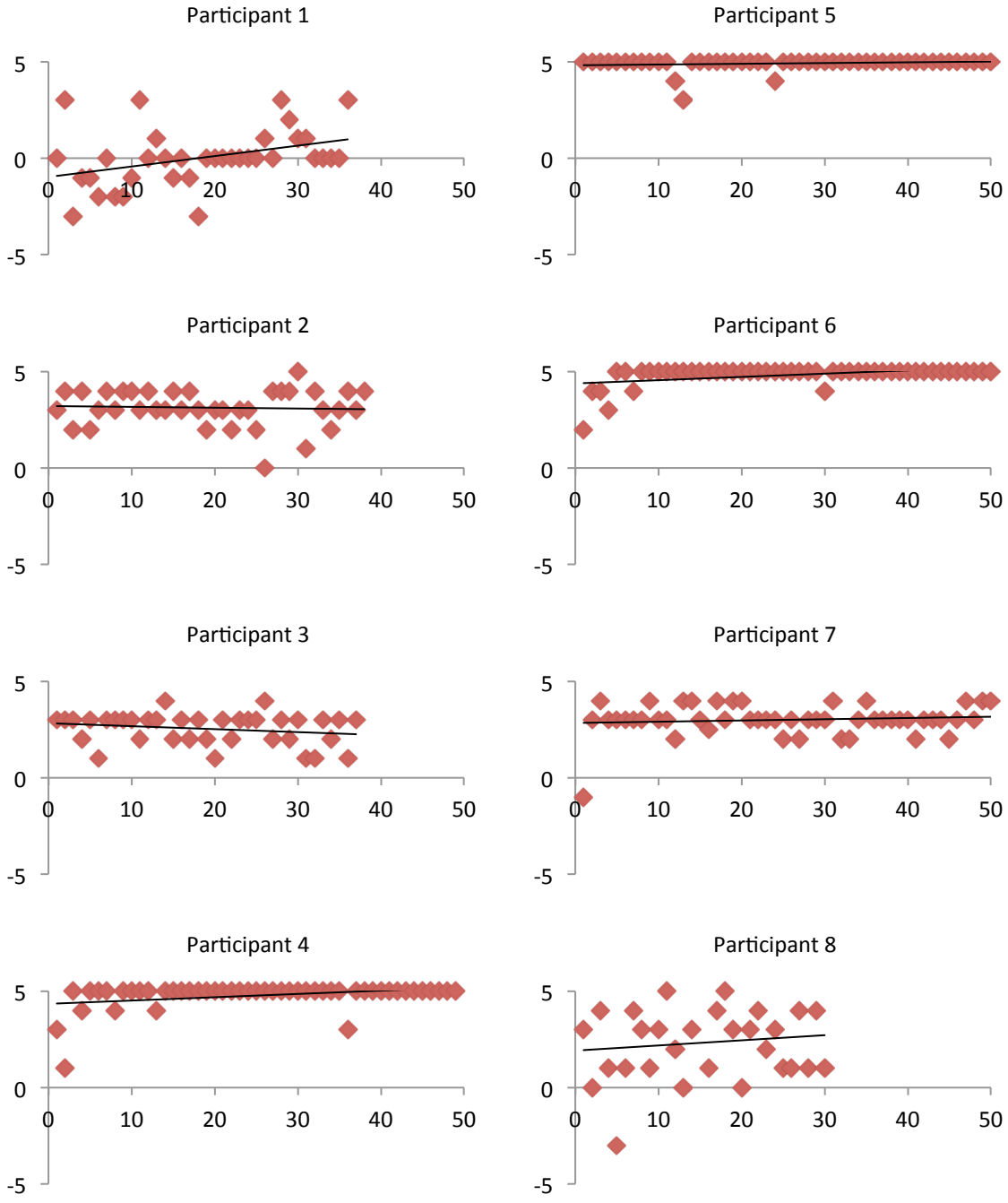
X-Axis: Class number
Y-Axis: Rating (0=No fatigue, 10=Strongest fatigue ever felt)

Post-Class Mental Fatigue

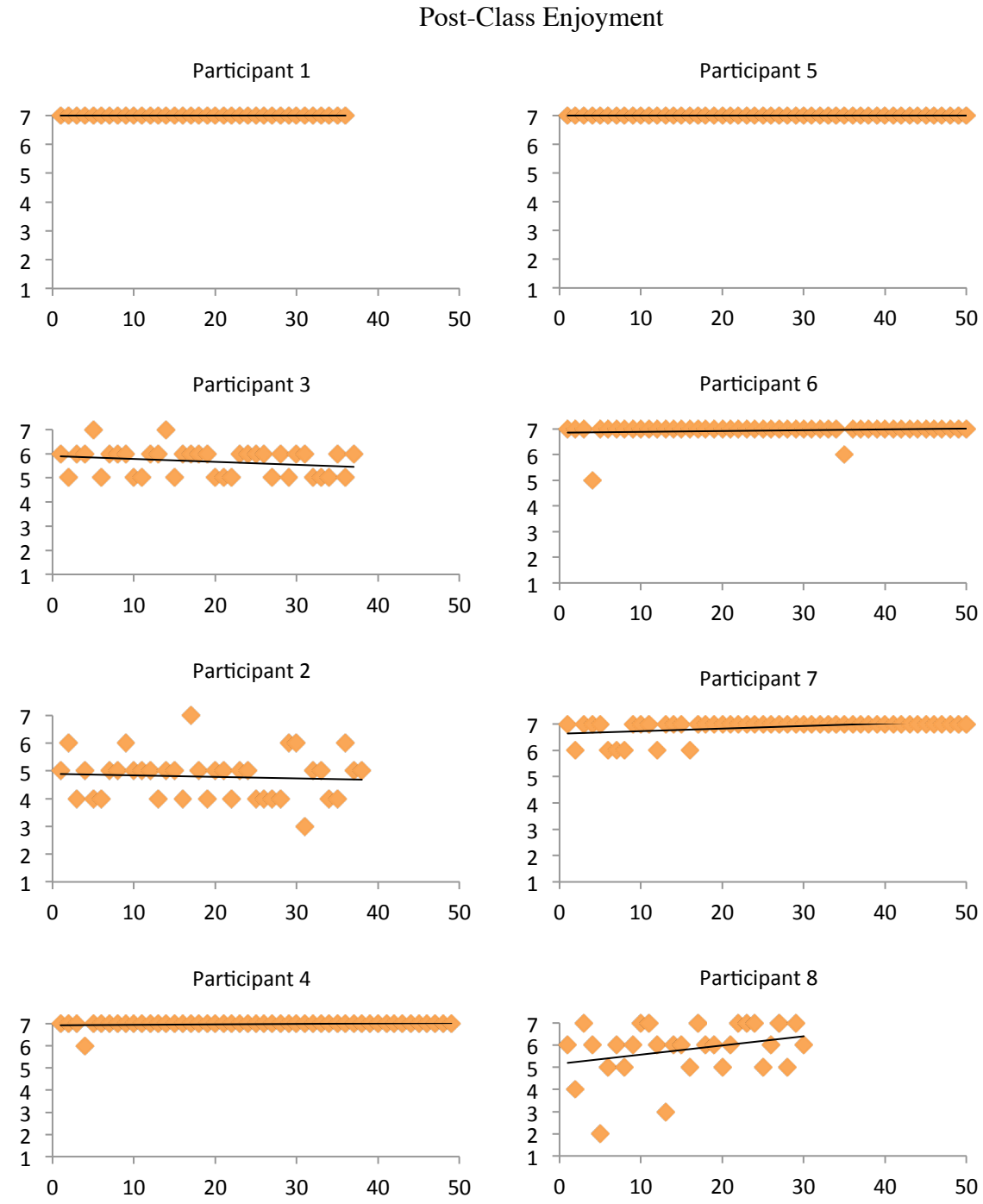


X-Axis: Class number
Y-Axis: Rating (0=No fatigue, 10=Strongest fatigue ever felt)

Post-Class Well Being



X-Axis: Class number
Y-Axis: Rating (-5=Very Bad, 0=Neutral, +5=Very Good)


Post-Class Enjoyment
Participant 1
Participant 5
Participant 3
Participant 6
Participant 2
Participant 7
Participant 4
Participant 8
X-Axis: Class number
Y-Axis: Rating (1=Not at all, 7=Very much)

APPENDIX F: PHYSICAL ACTIVITY CRITERIA

Godin Self-Report Criteria (2011).

	Intervention		
ID	**Baseline**	**T2**	**T3**
1	0	14	47
2	5	47	47
3	0	43	0
4	0	0	0
5	98	35	15
6	0	10	10
7	0	20	15
8	0	52	28
Total	1	5	5

	Control		
ID	**Baseline**	**T2**	**T3**
9	0	0	0
10	0	88	37
11	0	0	0
12	0	0	0
13	0	0	5
14	0	5	7.5
15	0	0	5
16	0	15	28
Total	0	2	2

Moderately active: 14 to 23 units (7 to 13.9 kcal/kg/week).
Active: > 24 units (~14 kcal/kg/week or more).

Canadian PA Guidelines for Persons with MS (2013).

	Intervention		
Baseline	**T2**	**T3**	
4	3	15	
25	37	30	
16	13	10	
11	16	7	
9	16	39	
19	17	11	
3	24	8	
23	43	14	
6	7	6	

	Control		
Baseline	**T2**	**T3**	
21	24	43	
4	8	3	
8	8	8	
6	11	11	
6	5	3	
4	3	13	
35	22	21	
12	6	4	
3	3	4	

Guideline criteria: >60 min/week (8.57 min/day) MVPA.

USDHHS PA Guidelines for Adults (2008).

	Intervention	
Baseline	**T2**	**T3**
4	3	15
25	37	30
16	13	10
11	16	7
9	16	39
19	17	11
3	24	8
23	43	14
2	3	2

	Control	
Baseline	**T2**	**T3**
21	24	43
4	8	3
8	8	8
6	11	11
6	5	3
4	3	13
35	22	21
12	6	4
1	2	1

Guideline criteria: >150 min/week (21.4 min/day) MVPA.

Met Moderately Active Criteria
Met Active Criteria

Met MVPA Criteria
Sandroff MVPA cut-off (2012)

Met MVPA Criteria
Sandroff MVPA cut-off (2012)

APPENDIX G: CES-D SCORES

Center for Epidemiological Studies Depression Scale

(CES-D)

	Intervention		
ID	**Baseline**	**T2**	**T3**
1	29	42	20
2	24	15	11
3	16	13	9
4	3	7	5
5	17	18	13
6	11	19	23
7	27	6	6
8	27	16	3

	Control		
ID	**Baseline**	**T2**	**T3**
9	6	7	8
10	6	15	9
11	28	28	28
12	15	19	16
13	6	7	7
14	5	7	6
15	7	4	14
16	33	12	30

Scores ≤ 15 "no depression"

Scores ≥ 16 "elevated depressive symptomatology"

(Radloff, 1977; Verdier-Taillefer et al., 2001)

APPENDIX H: REVIEW OF THE LITERATURE

Table 1.

Meta-Analyses Examining the Effect of Physical Activity on Cognition in Older Adults

Table 2.

Observational Studies of Physical Activity and Cognition in Persons with MS

Table 3.

Pre-experimental Studies of Physical Activity and Cognition in Persons with MS

Table 4.

Experimental Studies of Physical Activity and Cognition in Persons with MS

Table 1. Meta-Analyses Examining the Effect of Physical Activity on Cognition in Older Adults

Reference	Sample	RCTs	N	Independent Variable	Dependent Variables	Effects	Conclusions
Colcombe, 2003	Sedentary older adults ≥55 to 80 including clinical and non-clinical samples	18	197	Fitness training	• General cognitive performance • Executive control • Controlled processing • Visuospatial tasks • Speed tasks	• General cognitive performance (ES: 0.478, SE = 0.029, *n* = 101, p < .01) • Executive processes (ES: = 0.68, SE = 0.052, *n* = 37, p < .05) • Controlled tasks (ES: = 0.461, SE = 0.035, *n* = 74, p < .05) • Visuospatial tasks (ES: = 0.426, SE = 0.062, *n* = 23, p < .05) • Speed tasks (ES: = 0.274, SE = 0.050, *n* = 32, p < .05)	• Fitness training was associated with a significant improvement in general cognitive performance • Executive control benefitted the most from improved fitness followed by controlled, visuospatial, and speed tasks
Heyn, 2004	Adults ≥ 65 with cognitive impairment and dementia	30	2020	Exercise training	• Cognitive performance	• Cognitive performance (ES = 0.57, 95% CI: 0.43 − 1.17)	• Exercise training is associated with moderate effects on cognitive performance

Table 1. Meta-Analyses Examining the Effect of Physical Activity on Cognition in Older Adults (continued)

Smith, 2010	Non-demented adults ≥ 18 both healthy and with chronic conditions (MS, COPD, fibromyalgia)	29	2049	Aerobic exercise training	• Neurocognitive performance	• Attention and processing speed (ES = 0.158, 95% CI: 0.055 − 0.260, p = .003) • Executive function (ES = 0.123, 95% CI: 0.021 − 0.225, p = .018) • Memory (ES = 0.128, 95% CI: 0.015 − 0.241, p = .026) • Working memory (ES = 0.032, 95% CI: -0.103 − 0.166, p = .642)	• Aerobic exercise training has a modest effect on attention and processing speed, executive function, and memory but null effects on working memory
Hindin, 2012	Healthy, cognitively unimpaired adults ≥55	17	1016	Aerobic exercise training	• Untrained cognitive tasks	• Untrained cognitive tasks (ES: 0.325, 95% CI: 0.10 − 0.55, n = 89)	• Aerobic exercise training produced significant improvement in untrained cognitive tasks

Table 1. Meta-Analyses Examining the Effect of Physical Activity on Cognition in Older Adults (continued)

Gates, 2013	Adults ≥ 65 with mild cognitive impairment (MCI)	14	1695	Exercise training	• Cognitive function	• Verbal fluency (ES: 0.17, 95% CI: 0.04, 0.30) • Cognitive flexibility (ES: 0.13, 95% CI: -0.01, 0.27) • Response inhibition (ES: 0.12, 95% CI: -0.07, 0.31) • Delayed memory (ES: -0.01, 95% CI: -0.16, 0.14) • Information processing (ES: 0.57, 95% CI: -0.11, 0.42)	• Exercise training had a trivial but positive significant effect on verbal fluency but no significant effects on other measures of cognition

ES = Effect Size, SE = Standard Error, CI = Confidence Interval, COPD = Chronic obstructive pulmonary disease

Table 2. Observational Studies of Physical Activity and Cognition in Persons with MS

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Prakash, Snook, Erickson, et al., 2007	• Cross-sectional • N = 24	• 100% female • Definite RRMS • EDSS $\leq$ 6.0	Cardiorespiratory Fitness • VO_{2peak} (Cycle)	• Attention • Memory • Verbal learning and fluency • Delayed recall • Visuo-spatial learning • Sustained attention • Working memory • Information processing speed	• K-Bit • Wisconsin Card Sorting Test • Selective Reminding Test • Spatial Reminding Test • Symbol Digit Modalities Test • Paced Auditory Serial Addition Test (PASAT) • Word List Generation MRI • Paced Visual Serial Addition Test (fMRI)	Significant associations between level of cardiorespiratory fitness and - Information processing speed, sustained attention and working memory [PASAT] (r = 0.42) - Cerebrovascular function [fMRI] (r = 0.44 to 0.46), controlling for age, education, and MS duration in both

Table 2. Observational Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Prakash, Snook, Motl & Kramer, 2010	• Cross-sectional • N = 21	• 100% female • RRMS • EDSS $\leq$ 6.0	Cardiorespiratory Fitness • VO_{2peak} (Cycle)	• Gray matter volume • White matter integrity	MRI • T1- and T2-weighted images • Fractional anisotropy (FA)	Significant associations between cardiorespiratory fitness and brain tissue preservation while controlling for age and intracranial volume - Lesion load (r = -0.44) - Gray matter volume (r = 0.45) and - FA values (r = 0.40 to 0.44) controlling for age alone
Prakash, Snook, Kramer & Motl, 2010	• Cross-sectional • N = 82	• 83% female • RRMS • EDSS $\leq$ 7.5	Physical activity • Accelerometer (ActiGraph 7164) • Godin Leisure Time Exercise Questionnaire (GLTQ)	• Attention/concentration • Retrospective memory • Prospective memory • Planning/organization	• Perceived Deficits Questionnaire (PDQ)	Significant inverse relationship between perceived cognitive impairment (PDQ) and physical activity after removing variance associated with EDSS, FSS, CESD, MS duration and age measured by: - Accelerometer (r = -0.26) - GLTQ (r = -0.27)

Table 2. Observational Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Motl, Gappmaier, et al., 2011	• Cross-sectional • N = 33	• 66.7% female • Definite MS • Ambulatory • EDSS $\leq$ 7.0	Physical activity • Accelerometer (StepWatch - Step Activity Monitor)	• Processing Speed • Episodic memory • Learning	• Paced Auditory Serial Addition Test (PASAT) • Symbol Digit Modalities Test (SDMT) • Selective Reminding Test • Brief Visuospatial Memory Test-Revised	Physical activity significantly associated with composite score of cognitive processing speed (r = 0.35) after removing variance associated with age, education, gender, and MS duration

Table 2. Observational Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Prakash, Patterson, et al., 2011	• Cross-sectional • Post-hoc • N = 45	• 75.5% female • Clinically definite MS • EDSS ≤ 6.0	Physical activity • Accelerometer (ActiGraph GT3X)	• Relational memory • Hippocampus connectivity	• Modified item and relational memory task MRI • T2-weighted images	Significant association between physical activity and resting state hippocampal connectivity - posteromedial cortex: Left (r = 0.30) Right (r = 0.31) controlling for age, gender, education, MS duration and gray matter volume Left hippocampus-posteromedial cortex connectivity was associated with relational memory (r = 0.40, p = .006) in post-hoc analysis
Beier, Bombardier, Hartoonian, Motl, & Kraft, 2014	• Longitudinal • Post-hoc • N = 88	• 80.5% female • Clinically confirmed MS	Physical fitness • Bicycle ergometer	• Processing speed • Flexibility • Calculation ability • Divided attention • Working memory • Executive function	• Paced Auditory Serial Addition Test • Trail Making Test (TMT)	Significant time by group interaction for group with improved physical fitness on executive functioning (TMT-B, p = .05; TMT-BA, p = .02)

CES-D = Center for Epidemiologic Studies Depression Scale; EDSS = Expanded Disability Status Scale; fMRI = Functional Magnetic Resonance Imaging; FSS = Fatigue Severity Scale; VO_{2peak} = Peak oxygen consumption

Table 3. Pre-experimental Studies of Physical Activity and Cognition in Persons with MS

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Freeman & Allison, 2004	• One group pretest/posttest • N = 10 • 10-week attrition = not reported	• 80% female • Confirmed MS • EDSS $\leq$ 6.5	• Type - Supervised group floor exercise, posture & stretch program • Intensity – NR • Time (min) – 60 (30 min warm-up/cool-down) • Frequency (times/week) – 1 • Duration (weeks) - 10	• Fatigue (cognitive)	• Fatigue Impact Scale (cognitive subscale)	No significant changes in cognitive function related to fatigue
Roehrs & Karst, 2004	• One group pretest/posttest • N = 31 • 12-week attrition = 39%	• 65% female • Progressive MS • EDSS $\leq$ 8.0	• Type - Supervised group aquatic exercise program • Intensity – NR • Time (min) – 60 • Frequency (times/week) – 2 • Duration (weeks) - 12	• Attention • Retrospective memory • Prospective memory • Planning and organization	• Perceived Deficits Questionnaire	No significant change in perceived cognitive deficits

Table 3. Pre-experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Filipi et al., 2010	• One group pretest/posttest • N = 33 • 24-week attrition = not reported	• 67% female • Laboratory supported MS • EDSS $\leq$ 6.5	• Type - Supervised individual resistance training • Intensity – NR • Time (min) – 50 • Frequency (times/weeks) – 2 • Duration (weeks) - 24	• Attention • Memory	• Paced Auditory Serial Addition Test	Significant improvement in measure of attention and memory ($p < .01$)

EDSS = Expanded Disability Status Scale; HRQOL = Health Related Quality of Life; RRMS = Relapsing-Remitting Multiple Sclerosis; PPMS = Primary Progressive Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis, NR = not reported

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Velikonja et al., 2010	• Randomized prospective study • No control group • N = 20 • Group n - not reported • 10-week attrition = not reported	• Gender not reported • Relapsing-remitting or progressive MS • EDSS $\leq$ 6.0	• Type – Supervised group programs: 1. Sports climbing 2. Hatha yoga • Intensity – NR • Time (min) – NR • Frequency (times/week) – 1 • Duration (weeks) - 10	• Selective attention • Executive function	• Mazes subtest of Executive module from the Neuropsychological assessment battery • Tower of London Test • Brickenkamp d2 test • Modified Fatigue Impact Scale (cognitive subscale)	Significant improvement on selective attention after yoga (p = .005) and cognitive function (p = .024) related to fatigue after sports climbing

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Oken et al., 2004	• Randomized controlled trial • Wait-list control group • N = 57 • 22 yoga/15 aerobic exercise/20 wait list 24-week attrition = 17%	• 93% female • Clinically definite MS • EDSS ≤ 6.0	• Type – Supervised group programs 1. Iyengar yoga 2. Aerobic exercise (stationary cycling) • Intensity 1. Yoga: Poses held 10-30 seconds then rest for 30-60 seconds 2. Cycling: Light to moderate (RPE 2-3) • Time (min) 1. Yoga: 90 2. Cycling: 90 (10m warm up/cool down) • Frequency (times/week) – 1 + home practice • Duration (weeks) - 24	• Attention • Alertness • Mood • Anxiety • Fatigue (mental)	• Stroop Color and Word Test • Covert orienting of spatial attention task • Attentional shifting task • Modified Useful Field of View task, • Simple visual reaction time, • Paced Auditory Serial Addition Test, • Weschler Memory Scales III Logical Memory • Weschler Adult Intelligence Scale III Similarities • Multidimensional Fatigue Inventory (mental fatigue subscale)	No statistical effect on cognitive function measures in either intervention group

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Romberg et al., 2005	• Randomized controlled trial • Control group received no intervention • N = 95 • 47 intervention /48 control • 6-month attrition = 4%	• 64% female • Clinical or laboratory defined MS • EDSS ≤ 5.5	• Type *Week 1-3* Supervised group inpatient rehabilitation program: 5 sessions resistance training + 5 sessions aerobic exercise *Week 4-26* Home program: Resistance (Theraband®) training 3-4/week + aerobic training 1/week • Intensity – NR • Time (min) – NR • Frequency (times/week) – Week 1-3 – NR Week 4-26 – 5 • Duration (weeks) – 26	• Attention • Memory	Paced Auditory Serial Addition Test	No significant group x time interactions on measures of attention and memory

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Kargarfard et al., 2012	• Randomized controlled trial • Intention-to-treat analysis • Usual activity control group • N = 32 • 10 intervention/11 control • 8-week attrition = 34%	• 100% female • Relapsing-remitting MS • EDSS $\leq$ 3.5	• Type - Supervised group aquatic exercise program • Intensity – NR • Time (min) - 60 (20 min warm-up/cool-down) • Frequency (times/week) – 3 • Duration (weeks) - 8	• Fatigue - Cognitive • Cognitive function (HRQOL)	• Modified Fatigue Impact Scale (cognitive subscale) • MS-Health Related Quality of Life (cognitive function subscale)	Significant group x time effect on cognitive function related to fatigue (mean difference between baseline and 8-weeks = -1.9 $\pm$ 0.6, $p < .05$)

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Briken et al., (2013)	• Randomized controlled trial • Wait-list control group • Intention-to-treat analysis • N = 42 • 10 arm ergometry/11 rowing/11 bicycle ergometry/10 control • 8-10 week attrition = 10.6%	• 57% Female • 73.8% SPMS • 2.4% PPMS • EDSS ≤ 6.1	• Type – Individual exercise training programs 1. Arm ergometry 2. Rowing 3. Bicycle ergometry • Intensity – Mean Borg Scale = 4.6 • Time – NR • Frequency (times/week) – 2 to 3 • Duration (weeks) – 8 to 10	• Attention • Processing speed • Long-term memory • Executive function	• Symbol Digit Modalities Test • Verbal Learning and Memory Test • Test Battery of Attention • Achievement Testing System • Regensburg Verbal Fluency Test • Modified Fatigue Impact Scale (cognitive subscale)	Significantly improved verbal learning and delayed recall (p =.011) for all exercise groups; tonic alertness (p < .001) bicycle group; shift of attention (p = .026) arm and (p = .002) bicycle groups

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Pilutti, Dlugonski, Sandroff, Klaren, & Motl, 2014	• Randomized controlled trial • Wait-list control group • N = 82 • 37 intervention/ 39 control • 24-week attrition = 7.3%	• Female = 83.3% • RRMS = 79.3 % • SPMS = 12.1% • PPMS = 8.5% • PDDS 0-2 (mild disability) = 47.4% • Median PDDS = 3 (moderate)	• Type - Internet delivered theory-based program promoting physical activity • Intensity – NR • Time (min) – NR • Frequency (times/week) – NR • Duration (weeks) - 24	• Fatigue - Cognitive	• Modified Fatigue Impact Scale (cognitive subscale)	No significant group difference on cognitive function related to fatigue

Table 4. Experimental Studies of Physical Activity and Cognition in Persons with MS (continued)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Sandroff et al., 2014	• Randomized controlled trial • Wait-list control group • N = 82 • 37 intervention/ 39 control • 24-week attrition = 7.3%	• Female = 83.3% • RRMS = 78.9% • Progressive MS = 21.1% • PDDS 0-2 (mild disability) = 47.4% • PDDS 3-6 (moderate disability) = 52.6%	• Type - Internet delivered theory-based program promoting physical activity • Intensity – NR • Time (min) NR • Frequency (times/week) – NR • Duration (weeks) - 24	• Processing speed	• Symbol Digit Modality Test	Significant time x condition x disability group on processing speed for those in the intervention group with mild disability ($F_{1,66} = 5.68$, $p = 0.02$) moderate effect size ($\eta^2_p = 0.08$)

EDSS = Expanded Disability Status Scale; HRQOL = Health Related Quality of Life; RRMS = Relapsing-Remitting Multiple Sclerosis; PPMS = Primary Progressive Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; NR = not reported; RPE = rating of perceived exertion

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Vita

Janet Louise Dwight Morrison was born in Pasadena, California. After growing up in California, she moved with her family midway through her sophomore year in high school to the Washington DC area. She started her college education at Virginia Polytechnic Institute and State University in Blacksburg, Virginia majoring in biology. After two years at Virginia Tech, she transferred to George Mason University in Fairfax, Virginia where she graduated with a Bachelor of Science in Nursing and met her husband, Philip Wendell Morrison.

She spent the next 15 years in clinical practice as a perioperative nurse primarily working in the cardiac surgery in Virginia, California, and Maryland. While working in the cardiac OR at Johns Hopkins Hospital, she seized upon an opportunity to attend graduate school at Johns Hopkins University. During her final semester at JHU, she and her family moved back to San Diego, California. Thanks to the exceptional skills of her graduate advisor, Dr. Marie Nolan RN, PhD, FAAN, she was placed in mentorship with Dr. Barbara Riegel RN, PhD, FAAN at San Diego State University for her final semester in the masters program. She graduated from JHU with a Master of Science in Nursing, co-authored a paper about distance learning using a dial-up modem, and got her first job as a research assistant as a result of the move.

Less than a year later, another providential opportunity brought the family to Austin, Texas where an email sent to Dr. Alexa Stuifbergen RN, PhD, FAAN resulted in almost 20 years of learning how to be a nurse scientist from the best-of-the-best at the School of Nursing at The University of Texas at Austin.

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This dissertation was typed by Janet D. Morrison.